Effective Health Care Program

Comparative Effectiveness Review
Number 176

Management of Gout

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Comparative Effectiveness Review

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Addendum – October 2016

In the manuscript summarizing the findings of this report for journal submission, we performed an update search to March 2016. We identified 11 new publications meeting inclusion criteria. Incorporating these new studies did not change any conclusion or strength of evidence for any conclusion. More information is located in the Annals of Internal Medicine manuscript: http://annals.org/aim/article/doi/10.7326/M16-0461.

This report is based on research conducted by the RAND Southern California Evidence-based Practice Center (SCEPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2012-00006-I). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

None of the investigators has any affiliations or financial involvement related to the material presented in this report.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report may periodically be assessed for currency of conclusions. If an assessment is done, the resulting surveillance report describing the methodology and findings will be found on the Effective Health Care Program Web site at www.effectivehealthcare.ahrq.gov. Search on the title of the report.

Persons using assistive technology may not be able to fully access information in this report. For assistance contact EffectiveHealthCare@ahrq.hhs.gov.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Acknowledgments

The authors gratefully acknowledge Patricia Smith for her administrative support on the project.

Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

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In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report does not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential non-financial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential non-financial conflicts of interest identified.

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Management of Gout

Structured Abstract

Objectives. To review the evidence base for treating patients with gout, both acute attacks and chronic disease. The review specifically focuses on the management of patients with gout in the primary care setting.

Data Sources. We searched Medline, EMBASE, the Cochrane Collection, and the Web of Science using the search terms "gout," and "gouty," and terms for tophi (from January 1, 2010 to April 23, 2015, or at least one year prior to the search dates for the most recent systematic reviews). We also obtained relevant references from 28 recent systematic reviews that cover nearly all of the Key Questions. We searched Clinicaltrials.gov and the Web of Science for recently completed studies and unpublished or non-peer-reviewed study findings. Searches were not limited by language of publication.

Review Methods. We used standard systematic review methods including duplicate screening and data extraction from relevant studies, and existing tools to assess the quality of previously published systematic reviews, the risk of bias of individual studies, and the strength of evidence across studies.

Results. High-strength evidence supports the use of colchicine, nonsteroidal anti-inflammatory drugs (NSAIDs), and systemic corticosteroids to reduce pain in patients with acute gout. Moderate-strength evidence supports the use of animal-derived ACTH formulation for this condition. Moderate-strength evidence supports the finding that low-dose colchicine is as effective as higher-dose colchicine for treating acute gout attacks, and has fewer side effects. Evidence is insufficient from randomized controlled trials that assess symptomatic outcomes for specific dietary therapies. The evidence is also insufficient to support or refute the effectiveness of particular Traditional Chinese Medicine practices (e.g., herbal mixtures, acupuncture, and moxibustion) for symptomatic outcomes. High-strength evidence supports that urate lowering therapy (ULT, with allopurinol or febuxostat) reduces serum urate level. However low-strength evidence supports the finding that treating to a specific target serum urate level reduces the risk of gout attacks. High-strength evidence supports the finding that ULT does not reduce the risk of acute gout attacks within the first 6 months after initiation. However, moderate-strength evidence supports a role for ULT in reducing the risk of acute gout attacks after about 1 year of treatment. Low-strength evidence supports treating to a specific target serum urate level to reduce the risk of gout attacks. High-strength evidence supports the finding that prophylactic therapy with low-dose colchicine or low dose NSAIDs reduces the risk of acute gout attacks when beginning ULT. No criteria for when to discontinue ULT have been validated.

Conclusions. Effective treatments for acute gout include colchicine, NSAIDs, and corticosteroids/animal-derived ACTH formulation. Urate lowering therapy achieves its goal of lowering serum urate levels. Urate lowering should lead to a reduction in gout attacks, but the benefits and harms of long term urate lowering therapy have yet to be directly demonstrated. Patient preferences and other clinical circumstances are likely to be important in decisions about treating patients with gout.

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Executive Summary

Background and Objectives

Gout is the most common form of inflammatory arthritis and is characterized by acute intermittent episodes of synovitis presenting with joint swelling and pain (referred to as acute gouty arthritis, or acute gout attacks, or acute gout flares). It has been described as a disease of the foot since antiquity.[1] Approximately 8 million patients in the United States have gout. Gout is caused when excess urate in the body crystalizes (as monosodium urate [MSU]) in joint fluid, cartilage, bones, tendons, bursas or other sites. These crystals can directly stimulate an acute inflammatory attack. In some patients, acute gout attacks become progressively more frequent, protracted, and severe and may eventually progress to a chronic inflammatory condition. Additionally, in some patients the deposits of urate crystals grow into larger collections, called tophi (singular tophus) when clinically apparent.

The aim of this report is to review the evidence for the treatment of patients with gout, focusing on the primary care setting.

Etiology of Gout

Gout initially presents as an episode of acute inflammatory arthritis, most commonly involving the first meta-tarsal-phalanx joint, a condition commonly referred to as podagra. Typical attacks during the first few years last 7 to 14 days before resolving.

Although the primary risk factor for gout is hyperuricemia, not all patients with hyperuricemia go on to develop clinical gout; hyperuricemia that does not progress to gout is known as asymptomatic hyperuricemia. Patients with asymptomatic hyperuricemia may or may not have evidence of urate deposits in their joints (as documented by advanced imaging methods).[2]

The causes of gout are unclear but appear to be multifactorial, including a combination of genetic, hormonal, metabolic, and dietary factors. Family history, advancing age, male sex, or, in women, early menopause have been associated with a higher risk of gout and/or gout attacks (flares).[3] Some prescription medications such as thiazides are also believed to be risk factors for gout.

Diagnosis of Gout

A number of methods have been proposed to establish the diagnosis of gout. The evidence supporting the various methods for the diagnosis of gout is the subject of a separate systematic review.[4]

Clinical Presentation and Management

Gout encompasses both acute and chronic phases.

Acute Gouty Arthritis

The acute phase of gout is self-limited and characterized by recurrent attacks of synovitis (articular inflammation) that present with pain, erythema, and swelling, most frequently in the large toe but other joints, tendons, bursae or other areas may be involved.

Primary treatments for acute gout attacks have included non-steroidal anti-inflammatory agents (NSAIDs), corticosteroids (intraarticular), colchicine, and pituitary adrenocorticotropic hormone (ACTH, specifically animal-derived ACTH preparation) for the control of pain and inflammation.

Chronic Gout

Although initial episodes may be brief and rare, acute episodes may increase in frequency and duration over time and lead to the development of chronic gout. In addition to more frequent attacks, chronic gout may be associated with deposits of uric acid crystals known as tophi. Tophi may develop in joints, cartilage, bone, and auricular or other cutaneous tissues.[5] The average interval between the onset of gout and appearance of tophi, in the absence of treatment, is approximately 10 years.[5]

Management of chronic gout may include both pharmacologic and non-pharmacologic strategies. Historically, the treatment of chronic gout began with identification of patients as "overproducers" or "underexcretors" of uric acid, based on 24-hour urine collection. "Overproducers" were treated preferentially with allopurinol, whereas "underexcretors" were treated preferentially with the uricosuric probenecid. However, uricosuric agents may increase the risk of renal stones, requiring increased fluid intake and alkalinization for prevention. Probenecid use has fallen out of favor, because allopurinol was found to be effective in "underexcretors".[6, 7] Urate lowering strategies are the primary pharmacologic intervention for management of long-term complications of gout.

Lifestyle Changes

Non-pharmacologic methods advocated for management of chronic gout include a combination of lifestyle changes, including weight loss, exercise, hydration, and dietary changes. Such changes include reduction of dietary purines and alcohol intake, based on observational studies assessing associations between dietary components and risk for gout or trials assessing the effect of specific foods or supplements on serum uric acid levels. Dietary risk factors for gout have been postulated to include alcohol consumption, as well as consumption of meat, seafood, sugar-sweetened soft drinks, and foods high in fructose, whereas dairy foods and coffee have been associated with a lower risk of incident gout and in some cases a lower rate of gout attacks (flares). The evidence for the efficacy of specific dietary changes in managing gout (preventing attacks) is a topic of this review

Pharmacologic Agents

Pharmacologic management of chronic gout consists primarily of agents that lower serum urate. These agents include xanthine oxidase inhibitors (XOIs- allopurinol and febuxostat) to reduce serum urate production; uricosurics (probenecid), which prevent renal reabsorption of uric acid (and increase urinary uric acid excretion); and uricases, which stimulate the breakdown of uric acid (pegloticase). These agents can be used alone or in specific combinations (e.g., XOI plus probenecid). Pegloticase will not be included in this review because it would not be prescribed in a primary care setting (see below).

Table A lists the drugs used to treat gout and notes the ones covered in this systematic review.

Table A. Pharmacologic agents used in the treatment of gout

Drug Class	Agent (generic/brand)	Manufacturer
Anti-inflammatory Agents for Gout Attacks	NSAIDS (including Ibuprofen, naproxen, etodolac, diclofenac, indomethacin, COX-2 inhibitors)	Numerous
	Corticosteroids/ Animal-derived adrenocorticotropic hormone (ACTH) formulation	Numerous
	Colchicine/Colcrys™, Colchicine tablets, USP authorized generic	Takeda Pharmaceuticals, America, Inc.
	IL-1B Receptor Antagonists:[a] Anakinra/kineret®	Sobi
Urate Lowering Agents	Uricosurics: Probenecid/Benemid® or Probalan	Multiple
	Xanthine Oxidase Inhibitors: Allopurinol/Zyloprim®	Prometheus Labs
	Febuxostat/Uloric™	Teijin Pharma Ltd., Takeda
	Uricase: Pegloticase/Krystexxa®[a]	Crealta
	Combination agents: Colchicine-probenecid/Proben-C	Merck

[a]These agents will not be considered in this review, because they are not FDA-approved for use in treating gout and/or are not prescribed in the primary care setting.

Several interleukin-1ß-inhibitory anti-inflammatory agents currently approved for treatment of rheumatoid arthritis are in Phase II and III trials for treatment of gout, including anakinra, canakinumab, and rilonacept,[8-10] and will not be included in this systematic review, because they are not prescribed in the primary care setting (see below). These treatments do not act by lowering serum urate levels.

Additional off-label agents that have been proposed as useful in the management of gout include the lipid lowering agent, fenofibrate; the angiotensin 2 receptor blocker, losartan; estrogen; and calcium channel blockers (in patients being treated with these agents for other indications). These agents are not included in this review.

Scope and Key Questions

Scope of the Review

The purpose of this review is to assess the evidence on the management of patients with gout, in both the acute and chronic phases, including patients with tophaceous gout, and to assess management therapies that are FDA-approved and within the scope of practice of typical primary care providers. A protocol for the review was accepted and publicly posted on the AHRQ Web site on November 3, 2014 at: http://effectivehealthcare.ahrq.gov/ehc/products/564/1992/Gout-managment-protocol-141103.pdf.

Key Questions

The Key Questions (KQs) that guided this review are based on questions posed by the American College of Physicians (ACP). These questions underwent revision based on input from a group of key informants, public comments, and input from a Technical Expert Panel (TEP).

Key Question 1: Acute Gout Treatment

a. In patients with acute gout, what are the benefits and harms of different pharmacological therapies?
b. Does effectiveness (benefits and harms) differ according to patient baseline demographic characteristics and co-morbid conditions (including renal function)?
c. Does effectiveness (benefits and harms) differ according to disease severity, including initial clinical presentation (e.g., extent of joint involvement and time since start of flare) and laboratory values (serum and/or urine UA levels)?

Key Question 2: Dietary and Lifestyle Management of Gout

a. In adults with gout, what are the benefits and harms of different dietary therapies and life style measures on intermediate (serum and/or urine UA levels) and final health outcomes (including recurrence of gout episodes and progression [e.g., development of tophi])?
b. Does effectiveness and comparative effectiveness of dietary modification differ according to disease severity (including presence of tophi and baseline serum UA), underlying mechanisms of hyperuricemia, or baseline demographic and co-morbid characteristics?

Key Question 3: Pharmacologic Management of Hyperuricemia in Gout Patients

a. In adults with gout, what are the benefits and harms of different pharmacological therapies on intermediate (serum and/or urine UA levels) and long-term clinical health outcomes (including recurrence of gout episodes and progression)?
b. Does effectiveness and comparative effectiveness of urate lowering therapy differ according to disease severity (including presence of tophi and baseline serum UA), underlying mechanisms of hyperuricemia, or baseline demographic and co-morbid characteristics?
c. What is the effect of dietary modification in combination with pharmacologic therapy?

Key Question 4: Treatment Monitoring of Patients with Gout

a. In adults with gout, does monitoring serum urate levels with pharmacologic treatment and/or dietary and/or lifestyle change measures (e.g., compliance) improve treatment outcomes?
b. Is achieving lower subsequent serum urate levels (less than 5 vs. 5–7mg/dL) associated with decreased risk for recurrent acute gout attack, progression to chronic arthritis or disability, resolution of tophi, or other clinical outcomes (including risk for comorbidities or progression of comorbidities) or patient-reported outcomes?

Key Question 5: Discontinuation of Pharmaceutical Management for Patients on Acute or Chronic Gout Medications

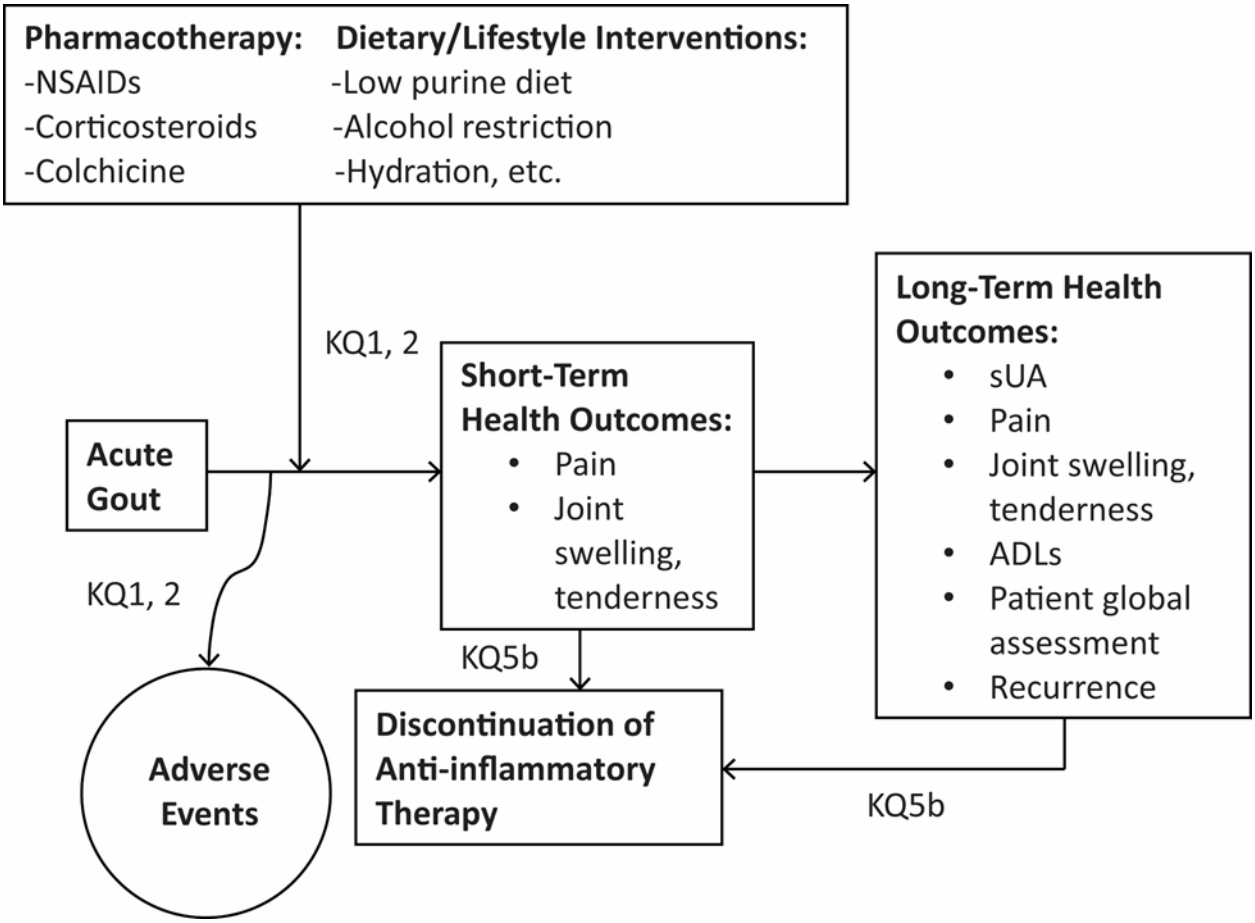
In adults with gout, are there criteria that can identify patients who are good candidates for discontinuing—

a. urate lowering therapy?
b. anti-inflammatory prophylaxis against acute gout attack for patients on urate lowering therapy after an acute gout attack?

Analytic Frameworks

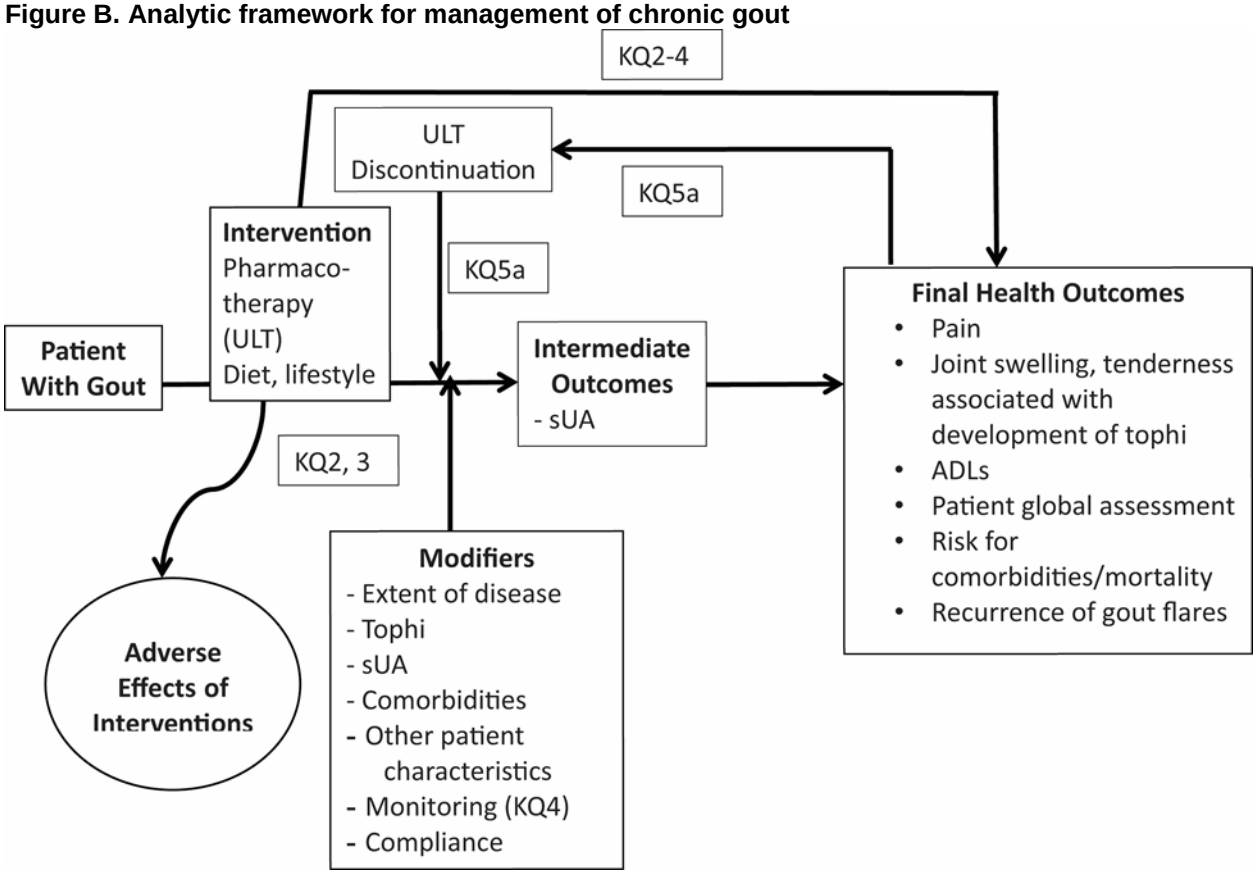
We provide two analytic frameworks: one for acute gout (Figure A) and one for chronic gout (Figure B).

Figure A. Analytic framework for treatment of acute gout



ADLs = activities of daily living; KQ = Key Question; sUA = serum uric acid; ULT = urate lowering therapy

Figure B. Analytic framework for management of chronic gout



ADLs = activities of daily living; KQ = Key Question; sUA = serum uric acid; ULT = urate lowering therapy

Methods

In general, this systematic review follows the procedures of the January 2014 edition of the "Methods Guide for Effectiveness and Comparative Effectiveness Reviews."[11]

Searching for the Evidence

We searched multiple databases for systematic reviews on gout and studies not included in those systematic reviews. In general, we include studies of effectiveness only if they were randomized controlled trials. If no trials could be identified of interest, observational studies were included for assessing the role of nutrition. Observational studies were also included for rare adverse events. Evidence obtained through the systematic review process was considered in light of what is already known about the physiology of gout and about the treatment of painful and inflammatory conditions.

Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions

We searched PubMed, EMBASE, the Cochrane Collection, and the Web of Science using the search terms "gout" and "gouty," and terms for tophi (January 1, 2010-April 23, 2015; at least one year prior to the search dates for the recent systematic reviews). We also obtained relevant references from at least 28 recent systematic reviews that cover nearly all of the KQs. We also

searched Clinicaltrials.gov and the Web of Science for recently completed studies and unpublished or non-peer-reviewed study findings. Searches were not limited by language of publication. We contacted manufacturers of the prescription medications used to treat gout that are listed in Table A for unpublished data specific to the use of these medications for treatment of gout or symptoms related to gout. We also included any relevant studies identified in the searches we conducted for a simultaneous review on diagnosis of gout if not already identified in the searches for this review. Finally, we asked the TEP to assess our list of included studies and to provide references for any additional studies they believed should also be included.

Data Abstraction and Data Management

Study level details from articles accepted for inclusion were abstracted by one reviewer and double checked by a second reviewer. Any disagreements were reconciled by the SCEPC Director, or the local subject matter expert if needed.

Assessment of Methodological Risk of Bias of Individual Studies

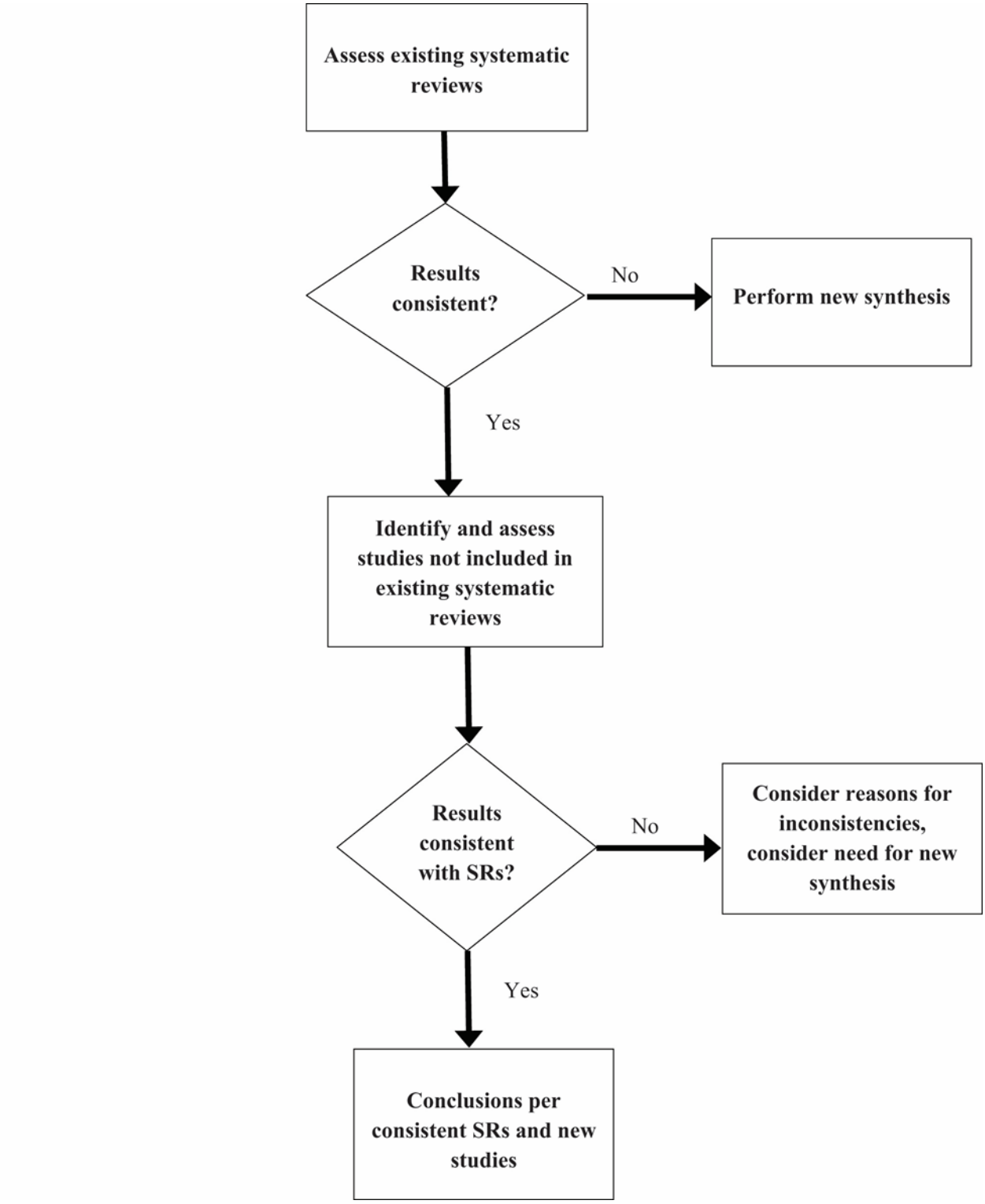
Risk of bias (study quality) of individual included studies was assessed independently by two reviewers using an adapted Cochrane Risk of Bias tool,[12] and assessments were reconciled, with any disagreements mediated by the project lead. We used a modified AMSTAR tool to assess the quality of existing systematic reviews that we included;[13] AMSTAR assessments were also conducted independently by two reviewers and reconciled.

Data Synthesis/Analysis

Given the large number of existing systematic reviews on this topic, we used the following strategy for data synthesis/analysis:

1. Identify the existing systematic reviews and make a judgment about relevancy for the KQs, the end date of the search, and the methodologic quality as assessed by AMSTAR,[13] following the process outlined by Whitlock and colleagues.[14]
2. Scan the references of these systematic reviews for included studies.
3. Search for new studies meeting the eligibility criteria for the KQ.
4. Compare the conclusions of the existing systematic reviews.
5. Compare the results of new studies with the conclusions of existing systematic reviews.
6. Use the guide shown in Figure C for additional analyses/conclusions.

Figure C. Framework for incorporating existing systematic reviews and studies not included in these reviews



SR(s) = systematic review(s)

Grading the Strength of Evidence (SoE) for Major Comparisons and Outcomes

We assessed the overall SoE for each conclusion (e.g., the efficacy and safety of each pharmacologic agent or class of agents listed in the PICOTs (Participants, Interventions, Control, Outcome, and Timeframe and Setting), and differences by subgroup, if identified), using guidance suggested by the Effective Health Care Program.[11] This method is based on one developed by the GRADE Working Group and classifies the grade of evidence as High (also called Strong), Moderate, Low or Insufficient. The evidence grade is based on five required domains: study limitations, consistency, directness, precision, and publication bias. The grades and their definitions are presented below.[11]

High: We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions

Moderate: We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.

Low: We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.

Insufficient: We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

We also considered in our strength of evidence assessments the criteria proposed by Bradford Hill for causality.[15] These criteria include the strength, consistency, and specificity of the association, the temporal relationship, the "biologic gradient" or dose-response curve, the biologic plausibility, and coherence. These principles allow us to construct and evaluate evidence chains. For example, in assessing the evidence regarding pharmacological urate lowering therapy (ULT) agents, we considered the biochemical properties of urate in serum: urate is soluble in serum up to a concentration of about 6.0-7.0mg/dl. Numerous cohort studies show a gradient of gout attacks related to increasing serum urate levels. RCTs of ULT have demonstrated evidence that they lower serum urate levels, but the longest trials have lasted only 6 to 12 months and have not shown reductions in acute gout attacks in part because the same pharmaceutical interventions increase the risk of acute gout attacks in the short term (months). Long term observational extension studies from these RCTs show that patients who continued on pharmaceutical therapy had reduced serum urate levels and after about 1 year, a < 5 percent risk of acute gout attacks. This evidence chain includes biologic plausibility, consistency of association, the appropriate temporal relationship, experimental evidence, the biologic gradient, and coherence. We rated this chain of evidence as moderate for pharmaceutical therapies to reduce the risk of acute gout attacks after about 1 year.

Assessing Applicability

Because the charge for this review is clear on the setting, care providers, and patient population the review is intended to cover, applicability assessment was based primarily on the similarity of the settings and populations to those for which this report is intended, namely primary and acute care settings that treat individuals, a high proportion of whom have comorbidities or are at risk for comorbidities such as hypertension and renal insufficiency.[16]

Peer Review and Public Commentary

A draft version of the report was posted for peer review on June 25 2015, and revised in response to reviewer comments.

Results

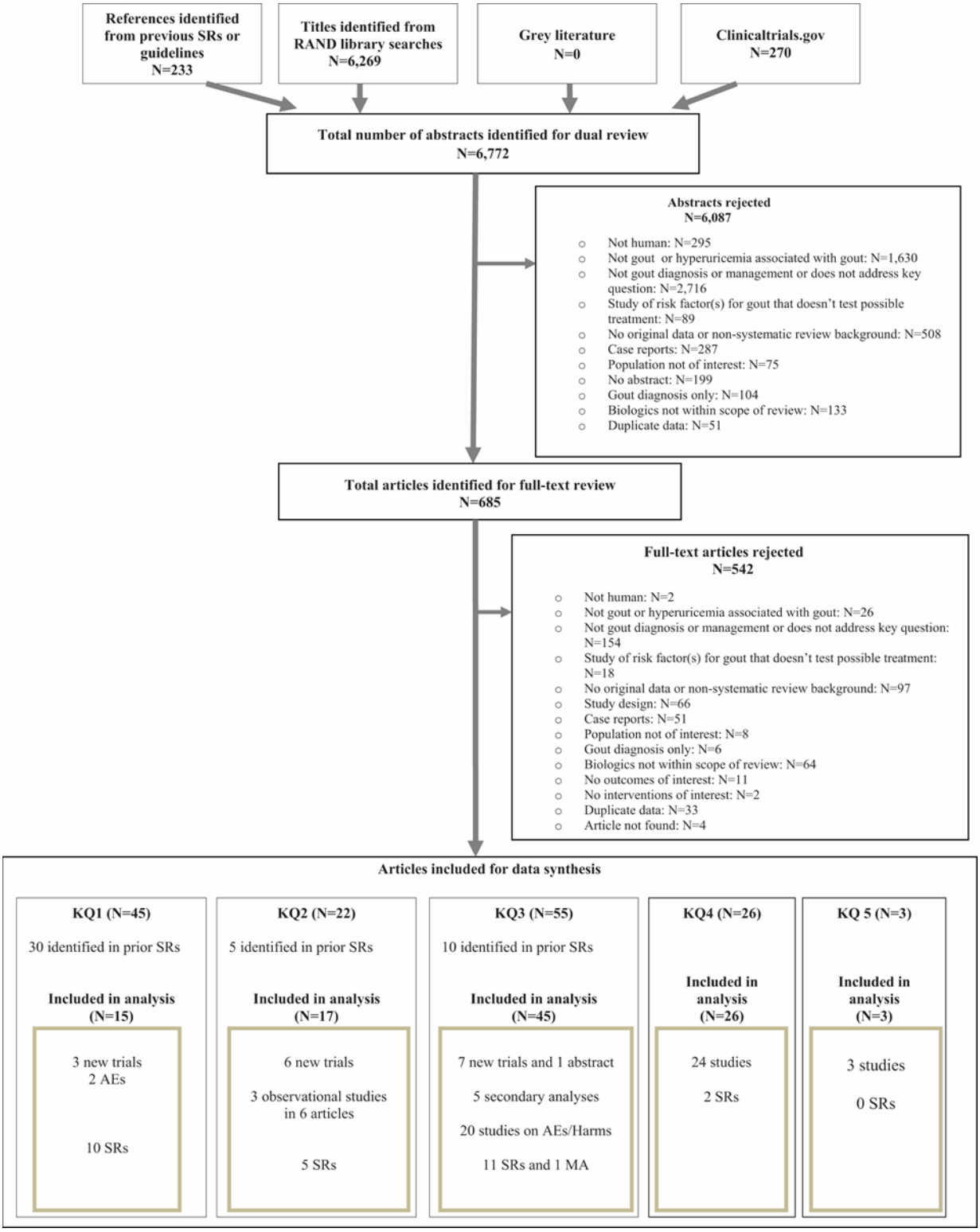
This section first describes the results of the literature searches, followed by descriptions of the studies that met inclusion criteria for each of the KQs and the key points (conclusions).

Results of Literature Searches

Our searches identified 6,269 titles/abstracts. Reference mining the previous systematic reviews (SRs) and guidelines identified in our searches resulted in an additional 233 titles. Our search of clinicaltrials.gov identified 270 entries for gout. Of these 19 were potentially relevant, 10 were either included already in our report or identified in our searches and excluded as ineligible, 1 was withdrawn, and 8 were recorded as being completed but no results were posted in clinicaltrials.gov, and we could find no published journal articles. Two manufacturers of drugs (Novartis and Regeneron) responded to requests by the AHRQ Scientific Resource Center for Scientific Information Packets on gout treatments. None of the trials described in these information packets was included in this report, as the drugs are currently not-FDA approved. Of a total of 6,772 titles/abstracts screened for inclusion. 6,087 titles/abstracts were excluded. At full text screening review, we rejected an additional 542 articles. Therefore, a total of 143 articles were included in our review.

For KQ 1, we included a total of 45 studies of which 15 were included in our analysis (3 RCTs, 2 studies that reported only on adverse events [AEs], and 10 systematic reviews [SRs]). The remaining 30 studies were identified in prior SRs. For KQ2, we included 22 studies of which 17 were included in our analysis (6 RCTs that examined dietary, lifestyle, Traditional Chinese Medicine [TCM] treatment, 3 observational studies [reported in 6 publications] on dietary factors, and 5 SRs). The remaining 10 studies were identified in prior SRs. For KQ3, we include a total of 55 studies of which 45 were included in our analysis (7 RCTs, 1abstract that has not been published, 5 secondary analyses, 20 studies that reported on AEs, 11 SRs and 1meta-analysis). The remaining 10 studies were identified in prior SRs. For KQ4, we include a total of 26 studies (24 original studies and 2 SRs). For KQ5, we include three original studies. See Figure D for the literature flow diagram.

Figure D. Literature flow diagram



AE(s) = adverse event(s); KQ = Key Question; MA = meta-analysis; RCT(s) = randomized controlled trial(s); SR(s) = systematic review(s)

Findings

The key findings and SoE are in Table B.

Key Questions 1a–c. Acute Gout Treatment

a. In patients with acute gout, what are the benefits and harms of different pharmacological therapies?
b. Does effectiveness (benefits and harms) differ according to patient baseline demographic characteristics and co-morbid conditions (including renal function)?
c. Does effectiveness (benefits and harms) differ according to disease severity, including initial clinical presentation (e.g., extent of joint involvement and time since start of flare) and laboratory values (serum and/or urine UA levels)?

Description of Included Studies

We identified 10 SRs on the following acute gout therapies: colchicine, NSAIDs, corticosteroids, and animal-derived ACTH formulation.[17-26] We further identified three new trials not included in previous SRs that met our inclusion criteria,[27-30] and two studies on adverse events (AEs).[31, 32]

Key Findings and SoE for Key Questions 1a–c

- High-strength evidence supports the efficacy of colchicine to reduce pain in acute gout.
- Moderate-strength evidence supports the finding that low-dose colchicine is as effective as higher dose for reducing pain, with fewer side effects.
- High-strength evidence supports the efficacy of NSAIDs to reduce pain in acute gout.
- Moderate-strength evidence supports a lack of difference among NSAIDs in effectiveness.
- High-strength evidence supports the efficacy of systemic corticosteroids to reduce pain in acute gout.
- Moderate-strength evidence supports animal-derived ACTH formulation to reduce pain in acute gout.
- SoE is insufficient regarding the effect of therapies on other outcomes: joint swelling, tenderness, activities of daily living, patient global assessment.
- SoE is insufficient regarding differences in efficacy stratified by patient demographic, comorbid conditions, disease severity, clinical presentation, or lab values.
- The most common adverse effects associated with colchicine are gastrointestinal symptoms, reported in 23 to 77 percent of users. NSAIDs also have gastrointestinal side effects, with dyspepsia or abdominal pain occurring in 10 percent or more of patients and more serious GI perforations, ulcers, and bleeds occurring in fewer than one percent of users, although the risk is greater in patients older than 65 years of age. Both colchicine and NSAIDs require dose reduction in renal impairment. The adverse effects of corticosteroids and animal-derived ACTH formulation are mostly related to long term use, although dysphoria, elevation in blood glucose, immune suppression, and fluid

retention may all occur, even with short term use, and cumulative doses from repeated short term courses may also cause harms similar to long term use.

Key Questions 2a–b. Dietary and Lifestyle Management of Gout

a. In adults with gout, what are the benefits and harms of different dietary therapies and life style measures on intermediate (serum and/or urine UA levels) and final health outcomes (including recurrence of gout episodes and progression [e.g., development of tophi])?
b. Does effectiveness and comparative effectiveness of dietary modification differ according to disease severity (including presence of tophi and baseline serum UA), underlying mechanisms of hyperuricemia, or baseline demographic and co-morbid characteristics?

Description of Included Studies

We identified five SRs that examined the efficacy of dietary and other lifestyle factors in the treatment of gout.[21, 33-36] In addition, we identified six original RCTs and three prospective observational studies (the latter described in six publications) not included in previous SRs that met our inclusion criteria and examined dietary and lifestyle interventions in gout management.[37-48]

Key Findings and SoE for Key Questions 2a–b

- The SoE from RCTs that assess symptomatic outcomes is insufficient to support a role for specific dietary changes (including reducing intakes of dietary purines, protein, or alcohol; increasing intakes of cherries, modified milk products, or supplemental vitamin C; or achieving weight loss) in gout management.
- The SoE is insufficient to support a role for gout-specific dietary advice (counseling about reducing red meat intake; avoiding offal, shellfish, and yeast-rich foods and beverages; and including low fat dairy products, vegetables, and cherries) compared with nonspecific dietary advice (counseling about the importance of weight loss and reduced alcohol intake) for reducing serum urate levels in patients with gout.
- The SoE is insufficient to support or refute the effectiveness of Traditional Chinese Medicine (TCM; including herbs and acupuncture) on symptomatic outcomes.

Key Questions 3a–c. Pharmacologic Management of Hyperuricemia in Gout Patients

a. In adults with gout, what are the benefits and harms of different pharmacological therapies on intermediate (serum and/or urine UA levels) and long-term clinical health outcomes (including recurrence of gout episodes and progression)?

b. Does effectiveness and comparative effectiveness of urate lowering therapy differ according to disease severity (including presence of tophi and baseline serum UA), underlying mechanisms of hyperuricemia, or baseline demographic and co-morbid characteristics?
c. What is the effect of dietary modification in combination with pharmacologic therapy?

Description of Included Studies

Our literature search identified 11 SRs[10, 49-58] and one meta-analysis.[59] In addition, we identified one new abstract[60] and five secondary analyses[61-65] of trials already included in the SRs and seven new trials.[30, 47, 66-70] For AEs, we included 20 studies.[71-90]

Key Findings and SoE for Key Questions 3a–c

- High-strength evidence supports the finding that urate lowering therapy does not reduce the risk of acute gout attacks in the first 6 months.
- Moderate-strength evidence supports a reduction in the risk of acute gout attacks after about 1 year of urate lowering therapy.
- High-strength evidence supports the efficacy of urate lowering therapy in reducing serum urate.
- High-strength evidence supports the finding of no difference between 40mg febuxostat and 300mg allopurinol in serum urate lowering.
- Evidence is insufficient about the potential effect of the presence of tophi on the effectiveness and comparative effectiveness of allopurinol and febuxostat.
- High-strength evidence suggests that prophylactic therapy with low dose colchicine or low dose NSAIDs when beginning urate lowering therapy reduces the risk of acute gout attacks.
- Moderate-strength evidence supports the finding that longer courses of prophylaxis with colchicine or NSAIDs (> 8 weeks) are more effective than courses of shorter duration to prevent acute gout attacks when initiating urate lowering therapy.
- The SoE is insufficient that gout-specific dietary advice adds to the effectiveness of urate lowering therapy in reducing serum urate.
- The most common adverse event associated with allopurinol is a skin rash, occurring in up to 5 percent of patients. While most of these are mild and reversible, serious skin reactions including Topic Epidermal Necrolysis and Stevens Johnson Syndrome have been reported. Allopurinol has been proposed as a cause of the DRESS syndrome (Drug Rash with Eosinophilia and Systemic Symptoms. These serious side effects are sufficiently rare that clinical trials lack power to detect them. The risk of DRESS is greatly increased in patients with the HLA-B*5801 allele. Some evidence indicates that allopurinol reactions are more likely to occur in the first six months of treatment.
- Clinical expertise with febuxostat is less than with allopurinol. The most commonly reported adverse events in trials of febuxostat were abdominal pain, diarrhea, and musculoskeletal pain (5 percent-20 percent for each), but these rates were not statistically

significantly different from those in placebo-treated patients. Rare skin reactions also occur with febuxostat.

- High-strength evidence supports a lack of difference in overall adverse events between allopurinol 300mg and febuxostat 40mg. A systematic review that identified four RCTs comparing the safety of urate lowering therapies found no statistically significant differences in overall adverse events between allopurinol and febuxostat.

Key Questions 4a–b. Treatment Monitoring of Patients With Gout

a. In adults with gout, does monitoring serum urate levels with pharmacologic treatment and/or dietary and/or lifestyle change measures (e.g., compliance) improve treatment outcomes?
b. Is achieving lower subsequent serum urate levels (less than 5 vs. 5–7mg/dL) associated with decreased risk for recurrent acute gout attack, progression to chronic arthritis or disability, resolution of tophi, or other clinical outcomes (including risk for comorbidities or progression of comorbidities) or patient-reported outcomes?

Description of Included Studies

For KQ 4a, we identified one SR[91] from which 16 original studies were referenced mined.[92-107]

For KQ 4b, we identified one SR[108] and eight studies that addressed the question.[109-116]

Key Findings and SoE for Key Question 4

- Evidence is insufficient to support or refute that monitoring serum urate improves outcomes.
- Low-strength evidence supports the finding that treating to a specific target serum urate level reduces the risk of gout attacks. However, the only way to know if urate lowering therapy affects serum urate is by monitoring serum urate levels. Therefore, this logic supports some monitoring, although how often and to what target have not been experimentally tested.

Key Question 5. Discontinuation of Pharmaceutical Management for Patients on Acute or Chronic Gout Medications

In adults with gout, are there criteria that can identify patients who are good candidates for discontinuing

a. urate lowering therapy?
b. anti-inflammatory prophylaxis against acute gout attack for patients on urate lowering therapy after an acute gout attack?

Description of Included Studies

We identified three observational (prospective cohort) studies[117-119] and also used data from three RCTs that addressed duration of anti-inflammatory prophylaxis in urate lowering therapy trials.[120-122]

Key Findings and SoE for Key Question 5

- The evidence is insufficient that discontinuing urate lowering therapy results in no increase in risk of acute gout attacks in gout patients who have completed 5 years of urate lowering therapy that kept serum urate levels < 7mg/dl, and in whom subsequent annual serum urate levels (off of urate lowering therapy) stayed < 7mg/dl.
- Moderate-strength evidence supports the finding that prophylaxis for acute gout with low dose colchicine or NSAIDs when initiating urate lowering therapy results in fewer gout attacks when treatment is given for longer than 8 weeks.

Discussion

Key Findings and SoE

We found a large number of research studies about gout, yet only a relatively modest number of these studies provided evidence for some of our KQs, particularly for the treatment of acute gout: only a single placebo-controlled trial of NSAIDs for acute gout pain, two placebo controlled RCTs of colchicine, and none at all for corticosteroids or ACTH. Nevertheless, we were able to reach strong conclusions about the usefulness of these drugs because of some specific features of gout: Symptoms result from an inflammatory reaction to the deposition of urate crystals, which occurs when serum urate rises above its saturation point in the blood. Hence, in an era that predated the widespread practice of placebo-controlled trial testing of therapies, medications aimed at blocking the inflammatory response were tried as treatments. Steroids are one of the most powerful and effective anti-inflammatory medications available. Although no placebo-controlled RCTs have tested their use in acute gout, steroids have proven efficacy in other inflammatory conditions, which gives us confidence that they are effective in treating the inflammatory reaction in acute gout. At this point, a placebo-controlled trial of steroids in acute gout may well be unethical, as it would mean withholding therapies of known effectiveness (e.g., colchicine) from the placebo-treated group. Indeed, a recent, high profile study of the use of steroids in acute gout compared their use not to placebo, but to NSAIDs. Because NSAIDs also have no conclusive placebo-controlled trial evidence of their effectiveness in acute gout, could it be that this RCT, which found only minor differences in outcomes between the two treatments, actually was comparing two treatments that were equally ineffective? We think not. We believe that both drugs are effective in treating acute gout, and therefore judged the SoE as high that their use relieves symptoms by a clinically important amount—despite the lack of placebo-controlled RCT evidence.

With regard to chronic gout, we similarly used evidence from a number of sources to reach conclusions about the effectiveness of ULT at reducing the risk of acute gout attacks over time, despite the fact that this outcome has not been studied in any placebo-controlled trial of longer than a few months. We based our moderate SoE rating on the high strength evidence that ULT reduces serum urate, that serum urate level is a strong predictor of the risk of acute gout attacks, and that the open-label extension studies of randomized controlled trials of ULT have shown a graded relationship between the serum urate level achieved and the risk of acute gout attacks. We thus concluded that over time, possibly by 1 year from initiation of therapy, ULT reduces the risk of acute gout attacks. We also concluded, based on a comparison of the timing of the occurrence of acute gout attacks in the weeks following initiation of ULT, that longer courses of prophylactic treatment with colchicine or NSAIDs (greater than 8 weeks) are more effective than courses of treatment with durations of 8 weeks or less, since in the one RCT of urate lowering

therapy where prophylactic colchicine or NSAIDs were continued for 6 months, no "spike" in acute gout attacks coincided temporally with the discontinuation of the prophylactic therapy, like that seen in other RCTs where prophylaxis was stopped at 8 weeks.

A third key finding of our review is that there is scant direct evidence about how much ULT to give (e.g. the concept of treating-to-a-target) and for how long to give it (are there any criteria about when ULT can be stopped, or if once started is treatment needed for life?).

The key findings and SoE are in Table B.

Findings in Relationship to What is Already Known

In general, our findings support the results of existing SRs. We did find a number of RCTs not included in prior reviews. Some of these studies were "first-of-their-kind," such as those testing a specific dietary therapy and the duration of colchicine prophylaxis. However, most new studies either confirmed prior knowledge, or, in the case of studies of novel treatments, were not sufficiently high quality for us to draw conclusions.

Applicability

Of the 115 studies assessed in detail (not counting SRs), only 9 studies explicitly stated that patients came only from, or the study included patients from, primary care sites (including the ED and urgent care settings). Furthermore, it is likely that patients enrolled in clinical trials differ from those commonly seen in primary care settings. In the major trials of ULT, the proportion of patients with tophi is greater than 20 percent[120-123] whereas in a trial that explicitly enrolled patients from primary care, the proportion of patients with tophi was 10 percent. A population-based study of more than 50,000 gout patients in English primary care practices reported the proportion with tophi as 0.5 percent[124] Patients enrolled in clinical trials usually have fewer comorbidities than those seen in practice, because clinical trials have exclusion criteria. Thus, in most trials, enrolled patients probably had more advanced gout, but were better on average with respect to their other health conditions, than patients typically seen in primary care settings. We thus judged this evidence of moderate applicability to primary care.

Implications for Clinical and Policy Decisionmaking

The implications of this review for clinical decision-making follow from the identification of which interventions for gout management have evidence of an effect on clinical outcomes, either directly or through a strong indirect evidence chain. Thus, the results in Table B will be useful in policy decision-making and in the development of practice guidelines.

Limitations of the Comparative Effectiveness Review Process

For many of the KQs of interest, data were not reported on the subgroups or outcomes of interest as specified in the KQs and analytic frameworks, limiting the comparative effectiveness review. For the portion of the review on Traditional Chinese Medicine (TCM), the variability in tested interventions made comparisons across studies not justified.

Limitations of the Evidence Base

The lack of studies specifically stating that they enrolled patients in primary care settings is a limitation, as is the lack of randomized controlled studies assessing clinical outcomes for ULT

(such as recurrent acute gout flare after 1 year) and intervention studies of dietary therapies for management of chronic gout. Longer term studies will be needed to assess the degree to which ULT reduces acute gout attacks relative to the adverse events of long term use of the available medications.

Research Gaps

The concept of "treat-to-target" (TTT) in gout, while supported by indirect evidence, has been untested. Guidelines and recommendations about TTT thresholds already vary, for example, < 6mg/dL for all gout patients versus < 5mg/dL for patients with significant gout morbidity. However, for many gout patients in primary care practice whose gout is well controlled on ULT, no data support such targets. In fact, the results of one cohort study suggest that once gout has been asymptomatic for 5 years, ULT might be discontinued for many years (as long as serum urate levels remain acceptable, e.g., < 7mg/dL).[117] Therefore, the most important research gap is a RCT comparing different TTT levels in patients with gout and elevated serum urate.

Treatment decisions are likely to be preference-sensitive, and studies are needed to assess patient preferences for different outcomes (for example, to what degree do patient preferences differ for outcomes such as a decrease in risk from 2 percent to 0.5 percent for an acute gout attack in the coming year versus a 5 percent chance of a skin rash and a less than 1 percent chance of a very serious skin rash).

Likewise, in spite of the many observational studies linking dietary factors with risk for gout, few studies have assessed the effect of specific dietary advice. Some dietary advice, such as generic advice to lose weight in overweight and obese patients, has evidence of benefit for other conditions and can be advocated in gout patients without additional data (e.g., it is always indicated to recommend dietary weight loss in patients who are obese). But primary care providers could more confidently recommend gout-specific dietary advice if compelling evidence supported an effect of such dietary changes on the risk for gout attacks or other gout-related outcomes. Therefore, another important research gap is evidence from RCTs for specific dietary changes (such as reducing or eliminating sugar-sweetened beverages or high-fructose foods, adequate hydration, restriction of alcohol, increase in low fat dairy consumption, and even restriction of high purine foods) compared with standard healthy diet advice and weight loss in reducing the risk of gout attacks.

A third research gap is the better characterization of adverse events from ULT and how they may be minimized. If the rare but serious adverse events from ULT could be further minimized, for example by HLA typing for predisposition, then the benefit/risk profile of ULT would further improve and make more patients eligible for treatment.

An additional research gap concerns prophylaxis when initiating ULT therapy. The optimal duration of such therapy has not been experimentally tested, and the comparative benefits/risks of all three agents used for acute attacks (colchicine, NSAIDs, oral steroids) have not been established.

Conclusions

Several drugs show moderate-to-high evidence of benefit in terms of reducing pain in patients with acute gout. It is clear that urate lowering therapy achieves its goal of lowering urate levels. Decreased serum urate should lead, over time, to a reduction in gout attacks, but the benefits and harms of long term urate lowering therapy have yet to be demonstrated directly.

Patient preferences are likely to be important in decision-making (as specified above), and having better estimates of the size of the benefit of urate lowering therapy will make clinicians and patients more knowledgeable about the risk: benefit trade-off for the different decisions.

Table B. Summary of prior knowledge, findings from the systematic review, and strength of evidence, by KQ

Key Question	Prior Knowledge Used in Determining Strength of Evidence	Sources of Evidence Included in This Systematic Review	Strength of Evidence
KQ1 Acute Gout Treatment			
Colchicine reduces pain	N/A	• 2 placebo-controlled RCTs (N=45 and N=184) both with low risk of bias	High
Low-dose colchicine is as effective as higher dose for reducing pain, with fewer side effects	N/A	• 1 head-to-head RCT with low risk of bias (N=184)	Moderate
NSAIDs reduce gout pain	• Biologic rationale (anti-inflammatory action) • Placebo-controlled RCT evidence that NSAIDs provide temporary pain relief for numerous conditions	• 1 placebo-controlled RCT with high risk of bias (N=30) • High strength observational data (NSAID use as prophylaxis against gout flare) (see below under KQ3)	High
No difference between NSAIDs in effectiveness	• Equivalence in effectiveness among NSAIDs in numerous other conditions	• 16 head-to-head RCTs	Moderate
Systemic corticosteroids reduce pain	• Biologic rationale (anti-inflammatory action)	• No placebo-controlled RCTs • Equivalence to NSAIDs in 4 RCTs (N=27, N=90, N=120, and N=60).Three of four RCTs had low risk of bias.	High
Animal-derived ACTH formulation reduces pain	• Biologic rationale (anti-inflammatory action)	• No placebo-controlled RCTs • Equivalence to NSAIDs and intramuscular steroids in RCTs (one RCT of each, N=76 and N=31 both at high risk of bias)	Moderate
Differences stratified by patient demographic, comorbid conditions, disease severity, clinical presentation, or laboratory values	N/A	None of the included RCTs presented data stratified by these variables.	Insufficient
KQ2 Diet and Lifestyle Management			
Specific dietary changes (including reducing intakes of dietary purines, protein, or alcohol; increasing intakes of cherries, modified milk products, or supplemental vitamin C; or achieving weight loss) in gout management may affect symptomatic outcomes	N/A	• 3 RCTs (two at high risk of bias) (N=67, N=120, N=40) • 3 observational studies (N=20, N=120, N=633)	Insufficient

Key Question	Prior Knowledge Used in Determining Strength of Evidence	Sources of Evidence Included in This Systematic Review	Strength of Evidence
Gout-specific dietary advice (counseling about reducing red meat; avoiding offal, shellfish, and yeast-rich foods and beverages or increasing low-fat dairy products, vegetables, and cherries) compared with nonspecific dietary advice (counseling about the importance of weight loss and reduced alcohol intake) for reducing serum urate levels in patients with gout	N/A	• 1 RCT with high risk of bias (N=30)	Insufficient
Effectiveness of Traditional Chinese Medicine (TCM) (acupuncture, herbal mixtures, moxibustion) on symptomatic outcomes	N/A	• 86 RCTs, all of idiosyncratic therapies, with conflicting results	Insufficient
KQ3 Management of Hyperuricemia			
Urate lowering therapy does not reduce the risk of acute gout attacks within the first 6 months	N/A	• 2 placebo-controlled RCTs,with low risk of bias (N=1,072 and N=57)	High
Urate lowering therapy reduces the risk of acute gout attacks after 1- year	• Acute gout attacks are caused by elevated serum urate concentrations	• No placebo-controlled RCTs assess long-term risk of acute gout attacks • RCTs with low risk of bias show that ULT reduces serum uric acid • Open label extension study of ULT RCT shows reduced risk of acute gout attacks over time, plateauing at less than 5% at about 1 year	Moderate
Urate lowering therapy reduces serum urate	N/A	• 4 placebo-controlled RCTs all with low risk of bias (N=1,072, N=96, N=153, and N=57)	High
40 mg febuxostat and 300mg allopurinol show no differences in serum urate lowering	N/A	• 1 head-to-head RCT with low risk of bias (N=2,269)	High
Effectiveness and comparative effectiveness of allopurinol and febuxostat depending on the presence of tophi	N/A	• Subgroup analyses of included trials did not report consistent results when stratified on the presence of tophi.	Insufficient
Age and race (Caucasian vs. African-American) do not affect the efficacy of febuxostat or allopurinol.	N/A	• Subgroup analyses of 1 head-to-head RCT with low risk of bias (N=2,269)	Low
Prophylactic therapy with low-dose colchicine or low-dose NSAIDs when beginning urate lowering therapy reduces the risk of acute gout attacks	N/A	• 1 placebo-controlled RCT of colchicine with low risk of bias (N=43) • Strong observational evidence across 3 RCTs with low risk of bias that included different durations of prophylaxis (N=762, N=2,269, and N=1,072)	High

Key Question	Prior Knowledge Used in Determining Strength of Evidence	Sources of Evidence Included in This Systematic Review	Strength of Evidence
Longer durations of prophylaxis with colchicine or NSAIDs (> 8 weeks) are more effective than shorter duration when initiating urate lowering therapy	N/A	• Indirect evidence from comparisons across 3 RCTs of differing durations of prophylaxis • 1 RCT with high risk of bias (N=190)	Moderate
Specific gout-dietary advice to reduce red meat, shellfish, etc. while increasing low-fat dairy products, vegetables, and cherries does not add to the effectiveness of urate lowering therapy for reducing serum urate	N/A	• 1 RCT with high risk of bias (N=30)	Insufficient
KQ4 Treatment Monitoring			
Serum urate monitoring improves outcomes	N/A	• No direct evidence • An argument can be made indirectly, based on the evidence that elevated serum urate levels cause gout	Insufficient
Treating to a specific target serum urate level reduces the risk of gout attacks	• Lower serum urate levels are associated with reduced risk of gout attacks	• No RCT evidence • Variable targets proposed or assessed in the literature	Low
KQ5 Criteria for Discontinuation of Pharmaceutical Management			
Hyperuricemia Urate lowering therapy may be discontinued in gout patients with 5 years of urate lowering therapy keeping serum urate levels <7mg/dl, with subsequent annual off-urate lowering therapy-serum urate levels <7mg/dl	N/A	• 3 prospective cohort studies (N=211, N=33, N=100)	Insufficient
Prophylaxis Prophylaxis for acute gout when initiating urate lowering therapy with low-dose colchicine or NSAIDs should be longer than 8 weeks	N/A	• Indirect evidence from comparisons across 3 RCTs with low risk of bias of differing durations of prophylaxis (N=762, N=2,269, and N=1,072)	Moderate

FDA = Food and Drug Administration; N/A = not applicable; NSAID = nonsteroidal anti-inflammatory drug; RCT = randomized controlled trial; ULT = urate lowering therapy

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Introduction

Background

Gout is the most common form of inflammatory arthritis and is characterized by acute intermittent episodes of synovitis presenting with joint swelling and pain (referred to as acute gouty arthritis, or acute gout attacks, or acute gout flares). It has been described as a disease of the foot since antiquity.[1] Approximately 8 million patients in the United States have gout. Gout is caused when excess urate in the body crystalizes (as monosodium urate [MSU]) in joint fluid, cartilage, bones, tendons, bursas, or other sites. These crystals can directly stimulate an acute inflammatory attack. In some patients, acute gout attacks become progressively more frequent, protracted, and severe, and may eventually progress to a chronic inflammatory condition. Additionally, in some patients, the deposits of urate crystals grow into larger collections, called tophi (singular tophus) when clinically apparent.

Based on data from the 2007-2008 National Health and Nutrition Examination Survey (NHANES), the prevalence of gout among adults in the United States was estimated to be 3.9 percent (8.3 million individuals), ranging from 2.0 percent in women to 5.9 percent in men.[2] Comparing the most recent figures for the prevalence of gout to those of previous cycles of NHANES shows that the prevalence of gout appears to be increasing. The rise in the prevalence of gout has paralleled the increase in prevalence of conditions associated with hyperuricemia, including obesity, hypertension, hypertriglyceridemia, hypercholesterolemia, type 2 diabetes and metabolic syndrome, and chronic kidney disease.[3] Certain dietary factors and medications also may increase the risk for developing gout (e.g., thiazide diuretics).

A 2013 study of ambulatory care costs associated with gout estimated the costs to be nearly $1 billion (in 2008 figures). Of this figure, 32 percent of the costs were attributed to office visits for acute attacks (flares), and 61 percent were attributed to expenditures for prescription medications to treat the condition.[4]

The aim of this report is to review the evidence for the efficacy and safety of treatments for patients with gout, focusing on the primary care setting.

Etiology of Gout

Gout initially presents as an episode of acute inflammatory arthritis, most commonly involving the first meta-tarsal-phalanx joint, a condition commonly referred to as podagra. Typical attacks during the first few years last 7 to 14 days before resolving. Over time, these attacks become prolonged and can become chronic. The acute gout attack is a result of urate (the salt form of uric acid [UA]) crystals directly interacting with the immune system. Several factors affect deposition of urate crystals, including temperature, local pH, and most critically, the concentration of serum urate. The solubility factor of urate is 6.8mg/dl; urate concentrations above this threshold lead to crystal deposition; levels below this threshold lead to crystal dissolution. UA is a breakdown product of dietary or endogenous purines, (which are among the building blocks of nucleic acids) and is associated with the formation and deposition of the UA crystals. Hyperuricemia can result from UA overproduction or inadequate renal excretion. The latter is far more common than the former, affecting 90 percent of patients: Renal disease and medications can affect the excretion of serum urate. As serum urate concentration rises above 6.0mg/dl, the risk for developing an acute gout attack increases. The Framingham Heart Study found that, among men, the 5-year incidence of acute gout attack increases from 10 percent when

serum urate is between 6.0 and 6.9mg/dl to 48 percent for serum urate greater than 8mg/dl.[5] Once a patient has had an initial attack, hyperuricemia increases the risk of repeat attacks. The 1-year incidence of recurrent attack is 30 percent for patients with serum urate between 6.0 and 6.9mg/dl and over 70 percent for patients with serum urate greater than 8mg/dl.[6] Although the primary risk factor for gout is hyperuricemia, not all patients with hyperuricemia go on to develop clinical gout; hyperuricemia in the absence of gout is known as asymptomatic hyperuricemia. Patients with asymptomatic hyperuricemia may or may not have evidence of urate deposits in their joints (as documented by advanced imaging methods).[7] The prevalence of hyperuricemia is about 21 percent, four-to ten-fold higher than the prevalence of gout.[2]

The causes of gout are unclear but appear to be multifactorial, including a combination of genetic, hormonal, metabolic, and dietary factors. Family history, advancing age, male sex, or, in women, early menopause have been associated with a higher risk of gout and/or gout attacks (flares).[8] Dietary risk factors are discussed further below. Some prescription medications such as thiazides are also believed to be risk factors for gout.

Diagnosis of Gout

A number of methods have been proposed to establish the diagnosis of gout. The evidence supporting the various methods for the diagnosis of gout is the subject of a separate systematic review.[9]

Clinical Presentation and Management

Gout is commonly divided into acute and chronic phases.

Acute Gouty Arthritis

The acute phase of gout is self-limited and characterized by recurrent attacks of synovitis (articular inflammation) that present with pain, erythema, and swelling, most frequently in the large toe, but other joints, tendons, bursae, or other areas may be involved.

A number of pharmacologic agents have been advocated for use in the management of acute gout. Commonly advocated agents to treat acute gout include non-steroidal anti-inflammatories (NSAIDS), colchicine (the microtubule disrupting agent), and/or corticosteroids (intra-articular or systemic) to manage pain and inflammation. The evidence for the efficacy of these agents in treating acute gout is a topic of this review.

Chronic Gout

Although initial episodes may be brief and rare, acute episodes may increase in frequency and duration over time and lead to the development of chronic gout. In addition to more frequent attacks, chronic gout may be associated with deposits of uric acid crystals known as tophi. Tophi may develop in joints, cartilage, bone, and auricular or other cutaneous tissues.[10] The average interval between the onset of gout and appearance of tophi, in the absence of treatment, is approximately 10 years.[10] Increased frequency of attacks and tophi are highly correlated with the presence of hyperuricemia. In addition to the aforementioned manifestations of chronic gout, patients with long standing gout can develop uric acid nephrolithiasis and chronic interstitial nephropathy. Gout has also been associated with a higher risk for progression of kidney disease[11] and increased risk of atherosclerotic disease, including myocardial infarction, heart failure, and stroke.[12]

Management of chronic gout may include both pharmacologic and non-pharmacologic strategies. Historically, the treatment of chronic gout began with identification of patients as "overproducers" or "underexcretors" of uric acid, based on 24-hour urine collection. "Overproducers" were treated preferentially with allopurinol, whereas "underexcretors" were treated preferentially with the uricosuric probenecid. However, uricosuric agents may increase the risk of renal stones, requiring increased fluid intake and alkalinization for prevention. Probenecid use has also fallen out of favor, because allopurinol was found to be effective in "underexcretors."[13, 14] Urate lowering strategies are the primary pharmacologic intervention for management of long-term complications of gout.

Lifestyle Changes

Non-pharmacologic methods advocated for management of chronic gout include a combination of lifestyle changes, including weight loss, exercise, hydration, and dietary changes, based on observational evidence that particular dietary and other lifestyle factors are associated with a greater or lesser risk for developing gout. Dietary risk factors for gout have been postulated to include alcohol consumption, as well as consumption of meat, seafood, sugar-sweetened soft drinks, and foods high in fructose, whereas dairy foods and coffee have been associated with a lower risk of incident gout and in some cases a lower rate of gout attacks (flares). Based on evidence that purines increase serum urate levels, avoidance of high–purine foods has been the mainstay of dietary management of gout for decades. Further evidence from recent trials and observational studies suggests that a number of additional dietary factors may affect the risk for gout or hyperuricemia.

A 2011 systematic review examined 53 observational studies that assessed the association of a variety of foods, other dietary factors, and other factors with the risk for incident gout.[8] Meat intake, seafood intake, consumption of alcohol, consumption of sugar-sweetened beverages and other high-fructose foods, and overweight were associated with an increased risk for gout. A 2013 5-year prospective cohort study of hyperuricemic Chinese men that used a food frequency questionnaire found a significant association between consumption of shellfish, but not other foods, and risk for gout.[15]

A 2012 systematic review that included 18 RCTs examined the effects of fructose intake on serum urate levels in normo-glycemic and diabetic patients. The review included both studies in which fructose isocalorically replaced other dietary components and those that added fructose to increase the caloric load. The review found no increase in serum urate with isocaloric fructose consumption but high levels of fructose that increased overall calorie intake increased serum urate.[16] Analysis of data from the large, observational Nurses' Health Study also found an association between consumption of fructose-sweetened beverages and increased risk for gout among women.[17]

The association between alcohol consumption and risk for incident gout was examined in a 2013 SR and meta-analysis that included 17 observational studies, reported in 12 articles.[18] Light (≤1 drink/day), moderate (>1 to <3 drinks/day), and heavy (≥3 drinks/day) drinking were associated with significant increases in the risk for gout, compared with non- or occasional drinking (RR1.16 (95 % CI, 1.07–1.25), 1.58 (95 % CI, 1.50–1.66), and 2.64 (95 % CI, 2.26–3.09), respectively. We also identified an additional study not included in the 2013 SR that assessed the association between alcohol consumption and risk for gout. ARIC, a 12-year prospective cohort study, identified an association between high levels of alcohol consumption and increased risk for incident gout.[19]

Studies have also identified dietary factors that reduce the risk for gout or lower serum urate levels. The 2011 systematic review by Singh found that consumption of dairy products and caffeine-containing beverages was associated with a decreased risk for gout.[8] Analyzing data from the Nurses' Health Study, Choi and colleagues also found that increasing coffee consumption was associated with a dose-dependent decrease in the risk for gout among women.[20] A 2011 SR by Juraschek and colleagues reviewed 13 trials on the effects of administration of vitamin C supplements on serum urate.[21] These trials enrolled a total of 556 participants, the median dosage of vitamin C was 500mg/day, trial size ranged from 8–184 participants, and the median study duration was 30 days. Pretreatment serum urate ranged from 2.9 to 7mg/dL. The pooled decrease in serum urate compared with placebo was a significant -0.35mg/dl (95% confidence interval -0.66, -0.03 [*P*=0.032]). Trials showed significant heterogeneity.

Risk for gout and gout-related outcomes have also been associated with obesity, body mass index, and weight loss. The systematic review by Singh found an association between low BMI and decreased risk for gout[8], and a 2014 systematic review that included 10 prospective studies found an association between increasing BMI and risk for gout.[22] The MRFIT trial, a prospective cohort study of U.S. men at increased risk for CVD found that weight loss was associated with decreased serum urate although less effective than ULT.[23] A recent RCT, the Dietary Intervention Randomized Controlled Trial (DIRECT), found that among 74 overweight and obese participants, a 6-month high-protein, low carbohydrate and low calorie diet resulted in significant weight loss and significant decrease in serum urate levels (0.8mg/dL, $p<0.0001$); among 18 whose baseline sUA was over 7mg/dL, 61 percent reached the target sUA level.[24]

The evidence for the efficacy of specific dietary changes in managing gout (preventing attacks) is a topic of this review.

Pharmacologic Agents

Pharmacologic management of chronic gout consists primarily of agents that lower serum urate. These agents include xanthine oxidase inhibitors (XOIs: allopurinol and febuxostat) to reduce serum urate production; uricosurics (probenecid), which prevent renal reabsorption of UA (and increase urinary uric acid excretion); and uricases, which stimulate the breakdown of uric acid (pegloticase). These agents can be used alone or in specific combinations (e.g., XOI plus probenecid). Pegloticase will not be included in this review because it would not be prescribed in a primary care setting (see below).

Table 1 lists the drugs used to treat gout and notes the ones covered in this systematic review.

Table 1. Pharmacologic agents used in the treatment of gout

Drug Class	Agent (generic/brand)	Manufacturer
Anti-inflammatory Agents for Gout Attacks	NSAIDS (including Ibuprofen, naproxen, etodolac, diclofenac, indomethacin, COX-2 inhibitors)	Numerous
	Corticosteroids/ animal-derived adrenocorticotropic hormone (ACTH) formulation	Numerous
	Colchicine/Colcrys™, Colchicine tablets, USP authorized generic	Takeda Pharmaceuticals, America, Inc.
	IL-1B Receptor Antagonists: [a] Anakinra/kineret®	Sobi
Urate Lowering Agents	Uricosurics: Probenecid/Benemid® or Probalan	Multiple
	Xanthine Oxidase Inhibitors: Allopurinol/Zyloprim®	Prometheus Labs
	Febuxostat/Uloric™	Teijin Pharma Ltd., Takeda
	Uricase: Pegloticase/Krystexxa®[a]	Crealta
	Combination agents: Colchicine-probenecid/Proben-C	Merck

[a]These agents will not be considered in this review, because they are not approved by the United States (US) Food and Drug Administration (FDA) for use in treating gout and/or are not prescribed in the primary care setting.

Several interleukin-1ß-inhibitory anti-inflammatory agents currently approved for treatment of rheumatoid arthritis are in Phase II and III trials for treatment of gout, including anakinra, canakinumab, and rilonacept;[25-27] these agents will not be included in this systematic review, because they are not prescribed in the primary care setting (see below). These treatments do not act by lowering serum urate levels.

Additional off-label agents that have been proposed as useful in the management of gout include the lipid lowering agent, fenofibrate; the angiotensin 2 receptor blocker, losartan; estrogen; and calcium channel blockers (in patients being treated with these agents for other indications). These agents are not included in this review.

Issues of Concern for Management of Gout in Primary Care Settings

The treatment of gout has spawned a proliferation of evidence-based guidelines,[28-34] including a recently completed set of guidelines by the American College of Rheumatology (ACR) that consider the treatment of both acute gout and hyperuricemia associated with chronic gout.[31,32]

However, the majority of individuals with gout are initially seen, diagnosed, and treated in primary care or emergent care settings and may continue to receive their care in these settings. Therefore primary care physicians (PCPs) and emergency physicians need to be well-positioned to diagnose early-stage gout and implement management strategies. It is established that specialists and generalists systematically rate the benefits and harms of treatment differently,[35] and in some instances, guidelines on the same clinical topic developed by specialists have had somewhat different recommendations than those developed by generalists.[36] Therefore, a new guideline, developed mainly by primary care practitioners and focused on primary care practice, is warranted. This review is intended to provide the evidence for such a guideline.

Scope and Key Questions

Scope of the Review

The purpose of this review is to assess the evidence on the management of patients with gout, in both the acute and chronic phases, including patients with tophaceous gout, and to assess management therapies that are FDA-approved and within the scope of practice of typical primary care providers. AHRQ assigned this report to the Southern CA Evidence-based Practice Center (HHSA290201200006I). A protocol for the review was accepted and publicly posted on the AHRQ Web site on November 3, 2014 at http://effectivehealthcare.ahrq.gov/ehc/products/564/1992/Gout-managment-protocol-141103.pdf. The protocol was approved by the AHRQ Center for Evidence and Practice Improvement.

Key Questions

The Key Questions

The Key Questions (KQs) that guided this review are based on questions posed by the American College of Physicians (ACP). These questions underwent revision based on input from a group of key informants, public comments, and input from a Technical Expert Panel (TEP).

Key Question 1: Acute Gout Treatment

a. In patients with acute gout, what are the benefits and harms of different pharmacological therapies?
b. Does effectiveness (benefits and harms) differ according to patient baseline demographic characteristics and co-morbid conditions (including renal function)?
c. Does effectiveness (benefits and harms) differ according to disease severity, including initial clinical presentation (e.g., extent of joint involvement and time since start of flare) and laboratory values (serum and/or urine UA levels)?

Key Question 2: Dietary and Lifestyle Management of Gout

a. In adults with gout, what are the benefits and harms of different dietary therapies and life style measures on intermediate (serum and/or urine UA levels) and final health outcomes (including recurrence of gout episodes and progression [e.g., development of tophi])?
b. Does effectiveness and comparative effectiveness of dietary modification differ according to disease severity (including presence of tophi and baseline serum UA), underlying mechanisms of hyperuricemia, or baseline demographic and co-morbid characteristics?

Key Question 3: Pharmacologic Management of Hyperuricemia in Gout Patients

a. In adults with gout, what are the benefits and harms of different pharmacological therapies on intermediate (serum and/or urine UA levels) and long-term clinical health outcomes (including recurrence of gout episodes and progression)?
b. Does effectiveness and comparative effectiveness of urate lowering therapy differ according to disease severity (including presence of tophi and baseline serum UA), underlying mechanisms of hyperuricemia, or baseline demographic and co-morbid characteristics?
c. What is the effect of dietary modification in combination with pharmacologic therapy?

Key Question 4: Treatment Monitoring of Patients with Gout

a. In adults with gout, does monitoring serum urate levels with pharmacologic treatment and/or dietary and/or lifestyle change measures (e.g., compliance) improve treatment outcomes?
b. Is achieving lower subsequent serum urate levels (less than 5 vs. 5–7mg/dL) associated with decreased risk for recurrent acute gout attack, progression to chronic arthritis or disability, resolution of tophi, or other clinical outcomes (including risk for comorbidities or progression of comorbidities) or patient-reported outcomes?

Key Question 5: Discontinuation of Pharmaceutical Management for Patients on Acute or Chronic Gout Medications

In adults with gout, are there criteria that can identify patients who are good candidates for discontinuing

a. urate lowering therapy?
b. anti-inflammatory prophylaxis against acute gout attack for patients on urate lowering therapy after an acute gout attack?

Organization of This Report

The remainder of this report presents the methods used to conduct the literature searches, data abstraction, and analysis for this review; the results of the literature searches, organized by KQ; the conclusions; and a discussion of the findings within the context of what is already known, the limitations of the review and the literature, and suggestions for future research.

Methods

Criteria for Inclusion/Exclusion of Studies in the Review

Included studies are limited to those that fit the PICOTS (below).

Studies in any clinical setting were included as long as they satisfied all other inclusion/exclusion criteria. The results of the report are intended for primary care and acute care settings, and therefore primary and acute settings are preferred. Case reports were excluded.

Studies were not limited by language. For studies of efficacy and effectiveness, we endeavored to include only randomized controlled trials. However, in the absence of relevant randomized controlled trials, observational studies were included. Observational studies were also included if they reported rare adverse events. Existing systematic reviews were also included both as sources of original data (reference mining) and for their conclusions, following the methods proposed by Whitlock and colleagues.[37]

PICOTS

- **Population(s)**
  - Adults (≥18 years of age) diagnosed with gout
    - Subgroups
      - Male and female patients (KQ1-5)
      - Patients presenting with an acute episode (KQ1, 2, 5) and those with a history of gout (KQ1-5)
      - Patients with higher versus lower serum UA (e.g., <5 vs. ≥5) (KQ1-5)
      - Patients who are HLA-B*5801-positive (KQ1) (HLA-B*5801 has been associated with an increased risk of allopurinol toxicity)
      - Older (≥65) versus younger patients (KQ1-5)
      - Tophaceous and non-tophaceous gout patients (KQ1-5)
      - Patients with comorbidities, including hypertension, Type 2 diabetes, chronic kidney disease (CKD) (renal insufficiency: CKD 1-4) (KQ1-5)

- **Interventions**
  - Dietary interventions (KQ2, 4)
    - Low purine diet
    - Fructose restriction, other carbohydrate restriction
    - Ethanol restriction
    - Sour cherry juice (proposed to be a XOI)
    - Dairy products and vegetables
    - Mediterranean diet
    - DASH (Dietary Approaches to Stop Hypertension) diet
  - Other Lifestyle Measures (KQ2, 4)
    - Exercise
    - Hydration
  - Dietary supplements and other alternative treatments (KQ2, 4)
    - Vitamin C

        - Traditional Chinese Medicine (acupuncture or Chinese herbal remedies: Ermiao wan, Meadow saffron, Dandelion, Burdock root; Huzhang gout granule; Jinhuang ointment; Yinlian gout granule, Si Miao San, Gout chi)
    - Pharmacologic agents
        - Acute gout treatment (KQ1, 4, 5b)
            - Anti-inflammatories (NSAIDS, corticosteroids [intra-articular and/or oral])
            - Microtubule inhibitors (colchicine)
            - Combination therapy (colchicine and NSAIDS/ oral corticosteroids; intra-articular corticosteroids/anti-inflammatories)
        - Urate Lowering Therapies (KQ3, 5a)
            - Xanthine oxidase inhibitors (XOIs: allopurinol, febuxostat) (KQ3, 5)
            - Uricosuric agents (probenecid) (KQ3, 5a)
        - Combination medications
            - Probenecid/colchicine (KQ3)
            - XOIs/anti-inflammatories (KQ3)
        - Co-interventions (KQ3-5)
            - Included pharmacologic agents plus included diet and life style measures (KQ2, 3,4)
            - Included pharmacologic agents and included Traditional Chinese Medicine interventions

- **Comparators**
    - Placebo or usual care (KQ 1, 3-5)
    - Active comparators (that are included interventions) (KQ1, 3-5)
    - Usual diet or level of activity or other dietary changes or dietary supplements that are included interventions (KQ2)
    - Early initiation of treatment (KQ 1, 2, 3)

- **Outcomes:**
    - For acute gout treatment (KQ1)
        - Efficacy
            - Short-term health outcomes (days following acute flare)
                - Pain
                - Joint swelling, tenderness
            - Longer-term health outcomes:
                - sUA
                - Pain
                - Joint swelling, tenderness
                - Activities of daily living (ADLs)
                - Patient global assessment
                - Recurrence
        - Safety
            - Gastrointestinal and renal side effects (NSAIDS, colchicine)
            - Steroid induced osteoporosis, diabetes

- For diet and other lifestyle therapy (KQ2)
  - Efficacy
    - Intermediate outcomes: serum and/or urine uric acid
    - Final health outcomes: recurrence and outcomes listed for pharmacologic treatments
  - Harms
- For chronic gout treatment (uric acid lowering therapy), monitoring, and discontinuation (KQ3-5)
  - Efficacy:
    - Intermediate outcomes: sUA
    - Final health outcomes: pain, joint swelling, tenderness associated with the development of tophi, ADLs, patient global assessment, risk for comorbidities/mortality, recurrence of gout attacks (flares)
  - Safety
    - Inflammatory effects, including skin rash
    - Hematologic effects
    - Cardiovascular effects
    - Liver dysfunction
    - Renal dysfunction
- For anti-inflammatory prophylaxis with ULT therapy (same outcomes as for acute gout therapy)

- **Timing**
  - Acute treatment (KQ1): 24-72 hours follow-up
  - Chronic treatment (KQ2-4): any follow-up time
  - Delayed versus immediate treatment (KQ1)

- **Setting (all KQ)**
  - Priority was given to patients being seen in primary care settings, which also includes urgent care clinics and emergency departments. If evidence from primary care settings was sparse, studies of patients in outpatient specialist settings were included

Searching for the Evidence

We searched multiple databases for systematic reviews on gout and studies not included in those systematic reviews. In general, we include studies of effectiveness only if they were randomized controlled trials. If no trials could be identified of interest, observational studies were included for assessing the role of nutrition. Observational studies were also included for rare adverse events. Evidence obtained through the systematic review process was considered in light of what is already known about the physiology of gout and about the treatment of painful and inflammatory conditions.

Literature Search Strategies for Identification of Relevant Studies To Answer the Key Questions

The search strategy was designed by our reference librarian in collaboration with our local content expert, who has participated in the two ACR systematic reviews on gout;[31, 32] the search strategy appears in Appendix A. We searched PubMed, EMBASE, the Cochrane Collection, and the Web of Science using the search terms "gout," and "gouty," and terms for tophi (January 1, 2010-April 23, 2015; at least one year prior to the search dates for the recent systematic reviews). We also obtained relevant references from at least 28 recent systematic reviews that cover nearly all of the KQs. We also searched Clinicaltrials.gov and the Web of Science for recently completed studies and unpublished or non-peer-reviewed study findings. Searches were not limited by language of publication; however, non-English language studies had to have an English language abstract in order to be screened. This process resulted in assessment of full text articles in the following languages: Chinese, French, German, Japanese, Spanish, Portuguese, and Russian. In addition, we contacted manufacturers of the prescription medications used to treat gout that are listed in Table 1 for unpublished data specific to the use of these medications for treatment of gout or symptoms related to gout.

We also included any relevant studies identified in the searches we conducted for a simultaneous review on diagnosis of gout if not already identified in the searches for this review. Finally, we asked the TEP to assess our list of included studies and to provide references for any additional studies they believed should also be included. An update search was conducted after submission of the draft report and studies identified in the update search underwent the same process.

The output of the literature searches was transferred to DistillerSR™ for screening. Article titles and abstracts identified by the searches were independently screened by two literature reviewers using the predetermined inclusion and exclusion criteria, and those selected by either reviewer were accepted without reconciliation for further, full-text review. Full-text review was also conducted independently by two reviewers to exclude articles that did not meet the inclusion criteria of the review. Disagreements regarding inclusion at the full-text stage were reconciled, with the input of the project lead when necessary.

We also identified a number of systematic reviews on gout management for which we performed reference mining. In addition, we searched the reference lists of included studies for additional titles that appeared to fit our inclusion criteria and screened these articles for inclusion.

Data Abstraction and Data Management

Study level details from articles accepted for inclusion were abstracted by one reviewer and double checked by a second reviewer. Any disagreements were reconciled by the SCEPC Director, or the local subject matter expert if needed.

Assessment of Methodological Risk of Bias of Individual Studies

Risk of bias (study quality) of individual included studies was assessed independently by two reviewers using an adapted Cochrane Risk of Bias tool,[38] and assessments were reconciled, with any disagreements mediated by the project lead. We used a modified AMSTAR tool to assess the

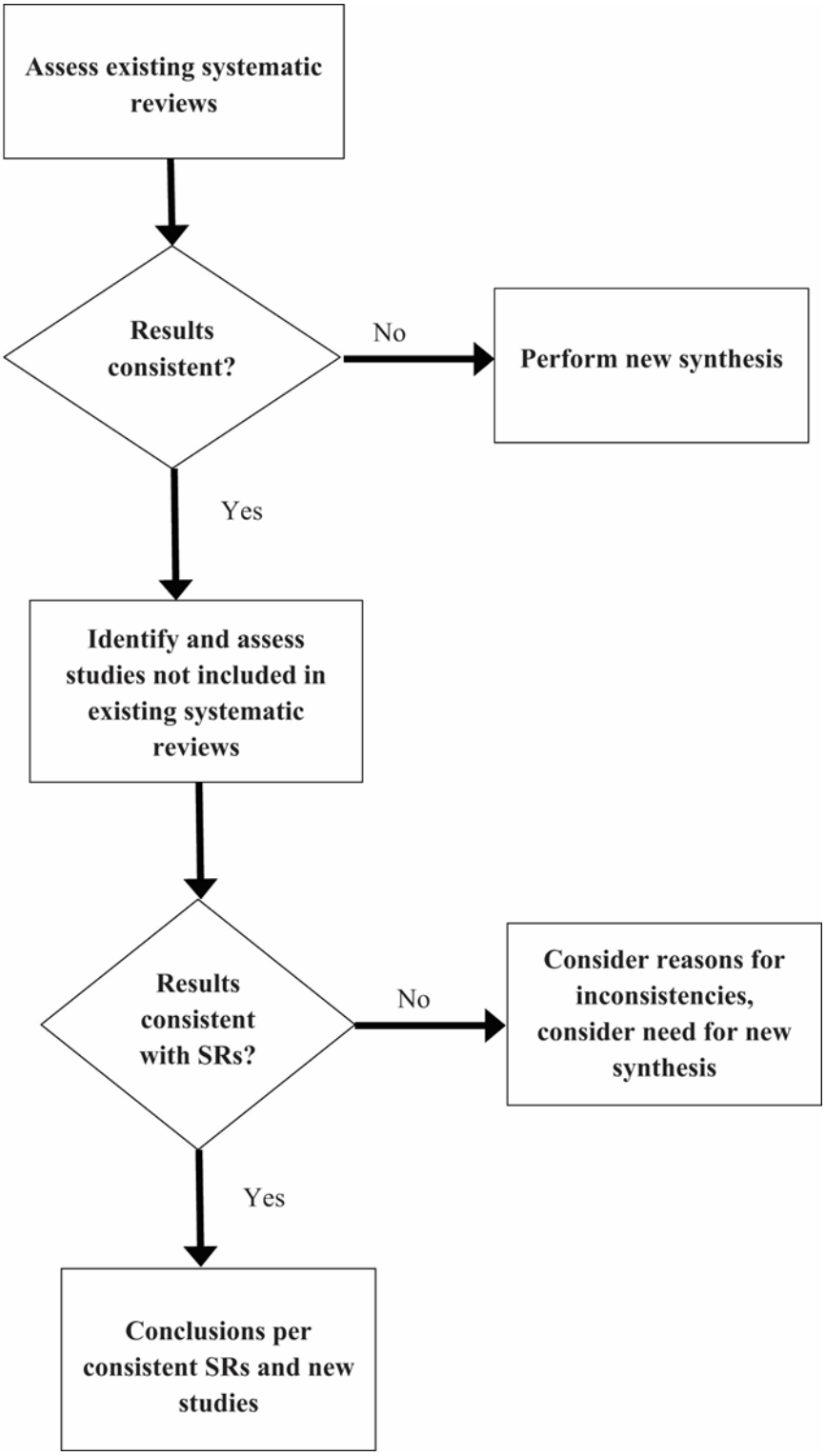
quality of existing systematic reviews that we included;[39] AMSTAR assessments were also conducted independently by two reviewers and reconciled.

Data Synthesis/Analysis

Given the large number of existing systematic reviews on this topic, we used the following strategy for data synthesis/analysis:

1. Identify the existing systematic reviews and make a judgment about relevancy for the KQs, the end date of the search, and the methodologic quality as assessed by AMSTAR,[39] following the process outlined by Whitlock and colleagues.[37]
2. Scan the references of these systematic reviews for included studies.
3. Search for new studies meeting the eligibility criteria for the KQ.
4. Compare the conclusions of the existing systematic reviews.
5. Compare the results of new studies with the conclusions of existing systematic reviews.
6. Use the guide shown in Figure 1 for additional analyses/conclusions.

Figure 1. Framework for incorporating existing systematic reviews and studies not included in these reviews



SR(s) = systematic review(s)

Grading the Strength of the Body of Evidence for Each Key Question

We assessed the overall SoE for each conclusion (e.g., the efficacy and safety of each pharmacologic agent or class of agents listed in the PICOTs, and differences by subgroup, if identified), using guidance suggested by the Effective Health Care Program.[40] This method is based on one developed by the GRADE Working Group and classifies the grade of evidence as High (also called Strong), Moderate, Low or Insufficient. The evidence grade is based on five required domains: study limitations, consistency, directness, precision, and publication bias. The grades and their definitions are presented below.[40]

High: We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions

Moderate: We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.

Low: We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.

Insufficient: We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

We also considered in our strength of evidence assessments the criteria proposed by Bradford Hill for causality.[41] These criteria include the strength, consistency, and specificity of the association, the temporal relationship, the "biologic gradient" or dose-response curve, the biologic plausibility, and coherence. These principles allow us to construct and evaluate evidence chains. For example, in assessing the evidence regarding pharmacological urate lowering therapy (ULT) agents, we considered the biochemical properties of urate in serum: urate is soluble in serum up to a concentration of about 6.0-7.0mg/dl. Numerous cohort studies show a gradient of gout attacks related to increasing serum urate levels. RCTs of ULTs have demonstrated evidence that they lower serum urate levels, but the longest trials have lasted only 6 to12 months and have not shown reductions in acute gout attacks, in part because the same pharmaceutical interventions increase the risk of acute gout attacks in the short term (months). Long term observational extension studies from these RCTs show that patients who continued on pharmaceutical therapy had reduced serum urate levels and, after about 1 year, a less-than-5 percent risk of acute gout attacks. This evidence chain includes biologic plausibility, consistency of association, the appropriate temporal relationship, experimental evidence, the biologic gradient, and coherence. We rated this chain of evidence as moderate for pharmaceutical therapies to reduce the risk of acute gout attacks after about 1 year.

Applicability

Because the charge for this review is clear on the setting, care providers, and patient population the review is intended to cover, applicability assessment was based primarily on the similarity of the settings and populations to those for which this report is intended, namely primary and acute care settings that treat individuals, a high proportion of whom have comorbidities or are at risk for comorbidities such as hypertension and renal insufficiency.[42]

Peer Review and Public Commentary

A draft version of the report was posted for peer review on June 25, 2015, and revised in response to reviewer comments.

Results

Introduction

This chapter first describes the results of the literature searches and then provides the results for each KQ, including key points, an overview of the studies identified for that question, and a detailed synthesis of the studies.

Results of Literature Searches

Our searches identified 6,269 titles/abstracts. Reference mining the previous systematic reviews (SRs) and guidelines identified in our searches resulted in an additional 233 titles. Our search of clinicaltrials.gov identified 270 entries for gout. Of these, 19 were potentially relevant, 10 were either included already in our report or identified in our searches and excluded as ineligible, 1 was withdrawn, and 8 were recorded as being completed but no results were posted in clinicaltrials.gov, and we could find no published journal articles. Two manufacturers of drugs (Novartis and Regeneron) responded to requests by the AHRQ Scientific Resource Center for Scientific Information Packets on gout treatments. None of the trials described in these information packets was included in this report, as the drugs are currently not FDA approved. Of a total of 6,772 titles/abstracts screened for inclusion. 6,087 titles/abstracts were excluded for the following reasons: not human (295), not gout or hyperuricemia associated with gout (1,630), not gout diagnosis or management or did not address a KQ (2,716), study of risk factor(s) for gout that doesn't test possible treatment (89), no original data or non-systematic reviews (508), case reports (287), population not of interest (75), titles with no abstracts (full-text articles or reports were obtained for a random sample of 10 percent of these titles and all were rejected as letters, commentaries, or non-systematic reviews with no original data, so on this basis, we decided not to consider the remainder) (199), gout diagnosis only (104),biologics not within scope of review (133), or duplicate data (51) (see Figure 2). We further reviewed 685 full text articles, of which 542 were excluded for the following reasons: not human (2), not gout or hyperuricemia associated with gout (26), not gout diagnosis or management or did not address a KQ (154), study of risk factor(s) for gout that doesn't test possible treatment (18), no original data or non-systematic reviews (97), study design (66), case reports (51), population not of interest (8), gout diagnosis only (6), biologics not within scope of review (64), no outcomes of interest (11), no interventions of interest (2), duplicate data (33), or article not found (4).

We considered 143 articles for data synthesis, which included 115 studies and 28 SRs.

For KQ 1, we identified 45 studies. Thirty studies were included in prior SRs. We included 10 systematic reviews (SRs), 3 randomized controlled trials (RCTs) not included in prior SRs, and 2 studies that reported only on adverse events (AEs).

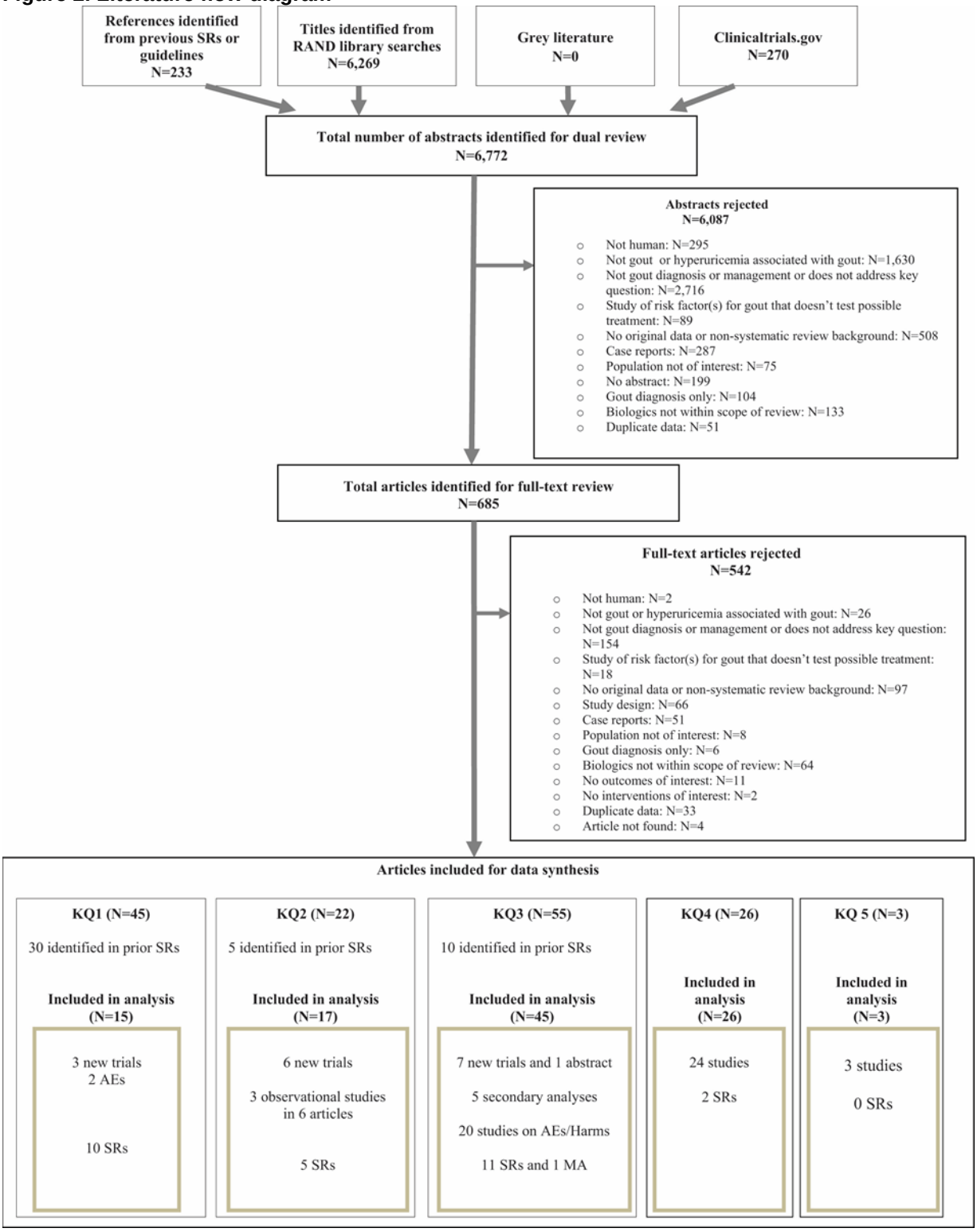
For KQ2, we identified 22 studies. Six studies were included in prior SRs. We include 5 SRs; 6 RCTs not included in prior SRs that examined dietary, lifestyle, and Traditional Chinese Medicine (TCM) treatments; and 3 observational studies (reported in six publications) on dietary risk factors.

For KQ3, we identified 55 studies. Ten studies were identified in previous SRs. We include 11 SRs and one meta-analysis, 7 RCTs not included in prior SRs and 1 abstract that has not been published, 5 new analyses of studies included in existing SRs, and 20 studies on AEs.

For KQ4, we include 2 SRs and 24 original studies. For KQ5, we include 3 original studies.

Figure 2 presents the literature flow diagram. Appendix B includes the reasons for exclusion of studies at the data abstraction phase.

Figure 2. Literature flow diagram



AE(s) = adverse event(s); KQ = Key Question; MA = meta-analysis; RCT(s) = randomized controlled trial(s); SR(s) = systematic review(s)

Key Questions 1a–c: Acute Gout Treatment

a. In patients with acute gout, what are the benefits and harms of different pharmacological therapies?
b. Does effectiveness (benefits and harms) differ according to patient baseline demographic characteristics and co-morbid conditions (including renal function)?
c. Does effectiveness (benefits and harms) differ according to disease severity, including initial clinical presentation (e.g., extent of joint involvement and time since start of flare) and laboratory values (serum and/or urine UA levels)?

Key Points

- High-strength evidence supports the efficacy of colchicine to reduce pain in acute gout.
- Moderate-strength evidence supports the finding that low-dose colchicine is as effective as higher dose for reducing pain, with fewer side effects.
- High-strength evidence supports the efficacy of NSAIDs to reduce pain in acute gout.
- Moderate-strength evidence supports a lack of difference among NSAIDs in effectiveness.
- High-strength evidence supports the efficacy of systemic corticosteroids to reduce pain in acute gout.
- Moderate-strength evidence supports animal-derived ACTH formulation to reduce pain in acute gout.
- SoE is insufficient regarding the effect of therapies on other outcomes: joint swelling, tenderness, activities of daily living, patient global assessment.
- SoE is insufficient regarding differences in efficacy stratified by patient demographic, comorbid conditions, disease severity, clinical presentation, or lab values.
- The most common adverse effects associated with colchicine are gastrointestinal symptoms, reported in 23 to 77 percent of users. NSAIDs also have gastrointestinal side effects, with dyspepsia or abdominal pain occurring in 10 percent or more of patients and more serious GI perforations, ulcers, and bleeds occurring in fewer than one percent of users, although the risk is greater in patients older than 65 years of age. Both colchicine and NSAIDs require dose reduction in renal impairment. The adverse effects of corticosteroids and animal-derived ACTH formulation are mostly related to long term use, although dysphoria, elevation in blood glucose, immune suppression, and fluid retention may all occur, even with short term use, and cumulative doses from repeated short term courses may also cause harms similar to long term use.

Description of Included Studies

We identified 10 existing SRs on the following therapies for acute gout: colchicine, NSAIDs, corticosteroids, and animal-derived ACTH formulation (see Table 2).[43-52] Five systematic reviews received an AMSTAR rating of either 7/7, 9/9, 10/10 (see Table 3).[43-45, 50, 52] Two

systematic reviews received an AMSTAR rating of 6/9[47] and 7/9.[51] Three reviews received an AMSTAR rating of 1/9 or 2/9.[46, 48, 49]

We also identified three new randomized-controlled trials, not included in existing SRs, that reported on the efficacy of agents to treat acute gout. These studies collectively involved 538 patients (range: 51 to 190 patients), with study time periods ranging from 5 days to 2 years. The primary outcomes of interest varied across studies, as shown in Table 4.[53-55] Two additional studies reported on AEs.[56, 57]

NSAID versus Intramuscular Glucocorticoid. One trial, involving 60 patients,[54] monitored self-reported pain intensity in the affected joint, patient's global assessment of response to therapy, physician assessment of joint swelling, serum urate levels, and adverse events.

NSAID versus Selective COX-2 Inhibitors. One trial, involving 178 patients,[53] monitored self-assessed pain, swelling and tenderness in affected joint, physician and patient assessment of global response to therapy, and number of withdrawals due to adverse events.

Colchicine + Allopurinol, over time. One trial, involving 190 patients,[55] monitored the probability of recurrence of gout attack, and the average time to recurrence. The patients were stratified by age, gender, and mean uric acid levels at baseline and follow-up.

Allopurinol versus Placebo (Colchicine as a prophylactic). One trial, involving 57 patients,[58] assessed pain on a visual analog scale (VAS) in the primary joint during days 1 – 10, the number of self-reported attacks (flares) in any joint through day 30, serum urate levels, sedimentation rates, and C-reactive protein levels.

Table 2. Randomized controlled trials included in systematic reviews

	Systematic Reviews									
RCTs	**Moi et al., 2013[44]**	**Janssens et al., 2008[45]**	**Richette and Bardin, 2010[48]**	**van Echteld et al., 2014[50]**	**Terkeltaub, 2008[49]**	**Daoussis et al., 2014[46]**	**van Durme et al., 2014[52]**	**Khanna et al., 2014[47]**	**Wechalekar et al., 2014[51]**	**Wechalekar et al., 2013[43] (Zero included studies)**
Ahern 1987[59]			X	X	X			X		
Alloway 1993[60]		X						X	x	
Altman 1988[61]							X	X		
Axelrod 1988[62]						X	X	X		
Borstad 2004[63]			X		X				x	
Butler 1985[64]							X	X		
Cheng 2004[65]							X	X	x	
Chou 1995[66]								X	x	
Douglas 1970[67]							X	X		
Eberl1983[68]							X	X	x	
Janssens 2008[69]							X	X	x	
Lederman 1990[70]							X	X		
Lomen 1986[71]							X			
Maccagno 991[72]							X	X		
Man 2007[73]		X					X	X		
Paulus 1974[74]			X							
Rubin 2004[75]							X	X	x	
Ruotsi 1978[76]								X		
Schlesinger 2002[77]	X							X		

	Systematic Reviews									
RCTs	**Moi et al., 2013[44]**	**Janssens et al., 2008[45]**	**Richette and Bardin, 2010[48]**	**van Echteld et al., 2014[50]**	**Terkeltaub, 2008[49]**	**Daoussis et al., 2014[46]**	**van Durme et al., 2014[52]**	**Khanna et al., 2014[47]**	**Wechalekar et al., 2014[51]**	**Wechalekar et al., 2013[43] (Zero included studies)**
Schumacher 2002[78]							X		x	
Schumacher 2012[79]							X	X		
Shi 2008[80]								X	x	
Shrestha 1995[81]							X	X	x	
Siegel 1994[82]		X				X		X	x	
Siegmeth 1976[83]							X			
Terkeltaub 2010[84]				X				X		
Tumrasvin 1985[85]									x	
Valdes 1987[86]								X	x	
Weiner 1979[87]								X		
Zhou 2012[88]							X			

Detailed Synthesis

Existing Systematic Reviews

Colchicine

Colchicine has been used as a treatment for gout since ancient times.[1] Six prior systematic reviews[44, 47-51] collectively identified 5 RCTs investigating the efficacy (pain reduction on VAS, number of acute gout attacks, and severity of attacks in terms of pain) and safety (total number of adverse events) of colchicine. Two of these studies were placebo-controlled trials of treatment for acute gout,[59, 84] two were placebo-controlled studies of prophylaxis against gout flare when initiating urate lowering therapy,[63, 74] and one study compared the addition of ice to colchicine and prednisone.[77] All reviews found that the proportion of colchicine-treated patients who reported a greater than 50 percent pain reduction was greater than that for placebo, especially if the treatment was administered within the first 12 hours of an acute attack.[44, 47-51] Low-dose colchicine (1.2mg initially followed by 0.6mg one hour later) was found to be as effective as high-dose colchicine (1.2mg initially followed by 0.6mg each hour for the next six hours) in terms of pain relief, but had a better tolerability profile in terms of gastrointestinal adverse events: 77 percent of participants who received high-dose colchicine developed diarrhea versus 23 percent in the low-dose group versus 14 percent in the placebo group.[84]

Systemic Corticosteroids

Identified systematic reviews did not find any placebo-controlled trials of systemic corticosteroids. Active-controlled trials of corticosteroids identified in the SRs are discussed in the section on comparative effectiveness.

NSAIDS

Two prior systematic reviews[51, 52] found one low-quality trial that compared the NSAID tenoxicam (40mg once a day) against placebo in 30 patients with gout. This study reported a significant between-group difference in the fraction of patients reporting greater than 50 percent pain relief at 24 hours, no between-group differences in joint swelling at 24 hours (11/15 in the tenoxicam group vs. 4/15 in the placebo group), and no overall between-group differences at day 4.[89] No difference in adverse events was reported among patients taking NSAIDs versus those taking the placebo.

Intra-articular Glucocorticoids

One prior systematic review[43] on intra-articular glucocorticoids identified no randomized trials for inclusion.

Comparative Effectiveness

Systemic Corticosteroids Versus ACTH

Three prior systematic reviews45, 47, 51 identified one RCT comparing systemic corticosteroids against adrenocorticotropic hormone (ACTH).82 In this trial 31 male patients with acute gout were randomized to receive either 40 IU of ACTH or 60mg triamcinolone intramuscularly. The study is not described as double-blinded. The duration of the acute attack

and the number of joints involved were not significantly different between the two groups, although the number of reinjections for continued symptoms were fewer in the triamcinolone group (14 vs. 6 p=0.075). No mention was made of side effects. We judged this trial as being at high risk of bias.

Systemic Corticosteroids Versus NSAIDs

Four prior systematic reviews[45, 47, 51, 52] identified three trials that compared the effectiveness of systemic corticosteroids against that of NSAIDs. None of the reviews found differences in terms of time-to-resolution of symptoms, clinical joint status at follow-up, reduction of pain at rest per hour during the first two hours and at rest per day after two weeks, and reduction of pain with activity per day after two weeks. Gastrointestinal, non-gastrointestinal, and severe adverse events were more common in the NSAID than in the systemic glucocorticoid group.[51]

NSAIDs Versus Selective COX-2 Inhibitors (COX-2)

Three prior systematic reviews[47, 51, 52] identified four controlled trials that compared NSAIDs against COX-2 inhibitors. COX-2 inhibitors were as effective as NSAIDs in terms of pain, joint swelling, global improvement, and health-related quality of life, but fewer withdrawals due to adverse events were observed among those treated with selective COX-2 selective inhibitors (3 percent) versus NSAIDs (8 percent) and fewer total adverse events were observed among the recipients of selective COX-2 inhibitors (38 percent) versus recipients of NSAIDs (60 percent). Low doses of selective COX-2 inhibitors were less effective in reducing pain than high doses, and NSAIDs were as effective as high-dose COX-2 inhibitors.[47]

NSAIDs Versus ACTH

Three prior systematic reviews[46, 47, 52] identified one trial comparing the efficacy of NSAIDs to ACTH for the treatment of acute gout.[62] In this randomized comparison of 40 IU intramuscular ACTH to 50 mg of indomethacin four times a day, among 76 (out of an initial sample of 100) men who completed 1 year of followup, the time to pain relief during an episode of acute gout was a mean of 3 hours in the ACTH-treated patients versus 24 hours in the NSAID-treated patients. No side effects were reported in the ACTH group, whereas 55 percent of patients in the NSAID group reported abdominal discomfort or dyspepsia, and 38 percent reported headaches. We judged this trial as being at high risk of bias.

NSAIDs Versus NSAIDs

We identified 16 RCTs that compared the efficacy of one NSAID versus another NSAID in patients with acute gout.[53, 61, 64, 65, 67, 68, 70-72, 75, 76, 78, 79, 81, 83, 87] Fifteen of these 16 studies were included in prior SRs. One new trial is described below.[53] Most of the studies were small and therefore underpowered to detect differences. Half of the studies enrolled fewer than 30 participants; only two studies enrolled more than 100 participants. Many of the NSAIDs studied are either no longer on the market or are not FDA-approved. Ibuprofen, which is one of the most-used NSAIDs in the US, was not assessed in any study. Most of the studies reported no statistically or clinically important differences between NSAIDs in effectiveness outcomes. These data do not support a hypothesis of clinically important differences between equipotent doses of NSAIDs in terms of relief of symptoms from acute gout, a conclusion that is compatible

with how NSAIDs are viewed for most other conditions, i.e., that their effectiveness is a class effect (see Table 5).

Evidence From New Eligible Studies

We identified three RCTs that were not included in any of the existing reviews (see Table 4).[53-55, 58]

Karimzadeh (2006)[55] assessed the optimal duration of prophylactic use of colchicine when initiating ULT. This study is discussed in detail in the description of the results for KQ 3.

Zhang (2014)[54] compared the efficacy of corticosteroids against that of NSAIDs in acute gout treatment, irrespective of gastrointestinal or cardiovascular risk factors. Sixty patients were randomized to receive either 7mg betamethasone intra-muscularly once during 7 days or 75mg diclofenac sodium twice a day for 7 days. The outcomes of treatment were pain intensity, tenderness, swelling and global assessment. Betamethasone had greater efficacy than that of diclofenac (measured as change from baseline percentage of patients reporting severe or extreme pain) on Day 3 and equivalent efficacy on Day 7. Fewer total adverse events were reported in the betamethasone group (4/30) than in the NSAID group (8/30), but statistical testing for difference was not performed. We judged this trial as being at low risk of bias.

Taylor 2012[58] investigated whether early initiation of allopurinol influenced the duration of acute gout attacks and pain associated with them. However we have not included this study in our response to this KQ as allopurinol was not included in the scope as a treatment in acute gout.

Li 2013[53] randomized a sample of 178 patients to either etoricoxib (120mg/day for 5 days), or indomethacin (75mg twice daily) for 5 days. No differences were seen between the two groups in self-assessed pain in the affected joint or in the total number of adverse events. We judged this study as being at low risk of bias.

The evidence from four new eligible studies is consistent with the conclusions of the systematic reviews.

Evidence About Subgroups

With one exception, we found no included studies that reported effectiveness stratified by any of the pre-specified subgroups of interest.

- Gender: No studies assessed the potential role of gender in response to treatment.
- Acute Episode: No studies assessed the potential effect of the duration of the acute episode on response to treatment.
- History of gout: No studies assessed the potential effect of the history of gout on response to treatment.
- Serum Urate: Karimzadeh (2006)[55] found no association between serum urate level and the probability of recurrence of gout attack when using colchicine prophylactically during ULT.
- HLA-B5801 status: No studies presented data stratified by HLA-B5801 status.
- Age: Karimzadeh 2006[55] also found no association of age with the probability of recurrence of gout attack when using colchicine prophylactically during urate lowering therapy.
- Tophi: No studies assessed the effect of the presence of tophi on response to treatment.
- Comorbidities: No studies presented data by comorbidities.

Harms

Fewer than 300 total gout patients were enrolled in the clinical trials that addressed this KQ. Yet these drugs have been in widespread clinical use for more than 30 years, not only for gout, but for numerous other conditions as well. A large body of evidence has been amassed on their harms, which has been summarized in various forms, including text books, systematic reviews, and online data sources. To ignore these data on the harms of these agents when used in other conditions would give readers an incomplete view of the body of evidence about harms. We therefore provide here brief summaries of the important harms of the major drugs for acute gout. Unless otherwise referenced, the data are compiled from Lexicomp, Medline Plus (www.nlm.nih.gov/medlineplus), and/or the FDA (http://www.fda.gov/Drugs/DrugSafety/default.htm).

Colchicine

The most common adverse effects associated with colchicine use, by far, are gastrointestinal side effects, in particular diarrhea, with reported rates of 23 percent to 77 percent. In the one placebo-controlled study of colchicine treatment for acute gout included in this review, the authors note that all patients had gastrointestinal side effects before they had relief of gout pain. Gastrointestinal side effects are dose dependent, which contributes to the popularity of "low dose" colchicine regimens.[84] Other gastrointestinal symptoms are also common, such as nausea, vomiting, cramps, and pain.[50] Fatigue and headache are reported in a small percent (1 percent-4 percent) of patients taking colchicine. Aplastic anemia has also been associated with colchicine. One analysis of VA databases calculated an adjusted hazard ratio of 3.32 (95% CI 2.32, 4.76) for aplastic anemia with colchicine use, and an incidence rate of 0.5/1000.[57] Another analyses of the FDA Adverse Event Reporting System found pancytopenia, renal failure, vomiting, and diarrhea as the most common reported adverse events, although without a denominator, no rate can be calculated.[56] According to the manufacturer, colchicine-induced neuromuscular toxicity and rhabdomyolysis have been reported with chronic treatment in therapeutic doses. Patients with renal dysfunction and elderly patients, even those with normal renal and hepatic function, are at increased risk. Dosage must be reduced in severe renal or hepatic impairment and with concomitant use of CYP3A4 inhibitors such as erythromycin and fluconazole and P-gp inhibitors like cyclosporine, and alternative therapies considered.

NSAIDs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used drugs in the world, and their safety profile allows for over-the-counter availability in low doses. The main harms attributed to NSAIDs are gastrointestinal side effects, both "minor" (dyspepsia) and more serious ("perforations, ulcers, and bleeds" [PUBs]," the former occurring in 10 percent or more of patients and the latter in up to 1 percent.[90, 91] PUBs are more common in older patients.[92] Another common adverse event associated with NSAIDs is reduced kidney function, occurring in 1 percent to 5 percent of patients, which can be acute kidney injury, worsening of hypertension, or electrolyte abnormalities. Mild-to-moderate renal impairment is a relative contraindication for NSAIDs use. NSAIDs are also reversible platelet inhibitors. Numerous other, rare, side effects have been reported, including bone marrow suppression, aseptic meningitis, and various dermatologic adverse events. NSAIDs have been associated with an increased risk of cardiac events including myocardial infarction, stroke, heart failure, and atrial

fibrillation and are the subject of FDA warning labels; however, in patients without known cardiovascular disease, the increase in risk is very small.

Corticosteroids

Long term use of glucocorticoids is associated with a host of adverse reactions, affecting almost every organ system of the body. However, most of these harms are dose and duration-dependent. The effects of short courses of glucocorticoids are not as well understood but include dysphoria and mood disorders, elevation of blood glucose levels, immune suppression, and fluid retention. All of these effects are reversible on discontinuation of the glucocorticoids, but low doses have cumulative effects over time: The cumulative effects of repeated short term exposures are similar to those seen with long term use.

ACTH

Although less used and well-studied than corticosteroids the mechanism of ACTH is in part via the stimulation of cortisol production by the body, Thus although ACTH is used and studies less than are corticosteroids, the expected harms are probably very similar to those for corticosteroids. In one trial of ACTH included here, no side effects were reported among 36 treated patients. The report of the other trial stated that the 14 patients who were treated with ACTH “tolerated [it] well.”

Strength of Evidence

Colchicine

We judged the strength of evidence that colchicine improves the symptom of pain in acute gout as high, because two placebo-controlled trials showed large (~50 percent reduction) effects.

NSAIDs

Only one placebo-controlled trial of an NSAID for treating acute gout was identified. However, we nevertheless judged the strength of evidence as high that NSAIDs improve the symptom of pain. We base this assessment on the biology of gout (it is an inflammatory reaction to uric acid crystals) and the mechanism of action of NSAIDs as an anti-inflammatory. Furthermore, NSAIDs are FDA approved for the temporary relief of pain, based on dozens of placebo-controlled trials for other painful conditions. Lastly, in patients starting on ULT, which is a risk factor for acute gout attacks, the strength of evidence is high (based on observational studies) that prophylaxis with NSAIDs greatly reduces this risk of an acute attack. Therefore, the evidence from the one available placebo-controlled trial is strengthened by the biological evidence and proven benefit in other painful conditions, and the large effect on prophylaxis against acute gout attacks with ULT. For comparisons of NSAID versus NSAID, while the available studies suffer from methodologic limitations, we found no signal of a differential effectiveness between NSAIDs, and this finding is compatible with the conclusions from other painful conditions that NSAIDs do not differ in effectiveness at equipotent doses. Thus we judged the SoE for this conclusion as moderate.

Systemic Corticosteroids

While we identified no placebo-controlled RCTs of systemic corticosteroids, we judged the strength of evidence that they reduce the symptom of pain in acute gout as high. This assessment

is based on the anti-inflammatory action of steroids and the equivalence in RCTs comparing systemic steroids to NSAIDs, which we judged as high strength of evidence in relieving pain.

ACTH

Although we identified no placebo-controlled RCTs of ACTH in acute gout, we judged the strength of evidence as high that it reduces the symptoms of pain in acute gout. Because a primary mechanism of action for ACTH is by increasing the body's release of corticosteroids, the reasons are the same as for corticosteroids. However, we downgraded the SoE to moderate as the only two equivalence trials were both judged as high risk of bias. In contrast, three low risk-of-bias equivalence trials assessed the efficacy of systemic corticosteroids.

Table 3. Systematic reviews of pharmacologic therapy for acute gout treatment

Author/Year/ Funding	End Date of Search	# of Included Studies	# of Included Patients/Patient Characteristics Included	Setting(s)	Outcomes	Doses	Results	AMSTAR
Richette and Bardin, 2010[48]; Colchicine/ Funding: T Bardin received honorarium from sanofi-aventis and Mayoly-Spindler.	Aug-10	3 RCTs	Not reported	Not reported	Proportion of patients with at least 50% reduction in pain within 24 hrs; Number of acute gout attacks	AGREE Trial: Placebo vs1.8mg colchicine vs. 4.8mg colchicine. RCT2: 500mg probenecid tid + 1.5mg colchicine vs. 500mg probenecid tid + placebo. RCT3: 0.6mg colchicine twice daily vs. placebo	Low-dose colchicine when given early as is effective as high-dose colchicine, in reducing pain and the number of acute gout attacks.	2/9
Janssens et. al., 2008[45]; Systemic corticosteroids/ Funding: Radboud University Nijmegen Medical Centre, Netherlands	Apr-07	3 head-to-head trials	148 patients; Patients of any age with acute gouty arthritis identified after MSU crystal identification or ACR criteria or clinical grounds	Hospital in-patient and out-patient	Patient assessment of pain and disability; investigator assessment of clinical symptoms; AE's	1. 60mg triamcinolone acetonide vs. 50mg indomethacin 2. 30mg oral prednisolone vs. 50mg indomethacin TID for 2 days, followed by 25mg TID for 3 days. 3. 60mg triamcinolone acetonide vs. 40 IU ACTH.	Inconclusive evidence for the efficacy and effectiveness of systemic corticosteroids compared with indomethacin in the treatment of acute gout. No AE's reported in the short-term.	9/9

Author/Year/ Funding	End Date of Search	# of Included Studies	# of Included Patients/Patient Characteristics Included	Setting(s)	Outcomes	Doses	Results	AMSTAR
Van Durme et. al, 2014[52]; NSAIDs, COX-2, ACTH, Oral glucocorticoids/ Funding: In-kind support by: Masstricht University Medical Center, Flinders University, UMNDJ, Cabrini Hopsital, Monash University, Leiding University Medical Center, Atrium Medical Centre, University of Amsterstam	10/7/2013	23 RCTs	N = 2200 / adults 18+ with a diagnosis of acute gout	Outpatients	Proportion of participants with >= 50% pain improvement; Proportion of participants with >=50% inflammation or joint swelling improvement; Functioning of target joining; HRQoL; Participant withdrawal due to AE's. Total number of AE's.	NSAID (40mg) vs. placebo (N=1) NSAID vs. NSAID (N=13) NSAID (50mg indomethacin x3) vs COX2 (etoricoxib 120mg x1 or celecoxib 50mg, 200mg or 400mg x2 or lumiracoxib 400mg x1) (N=4); NSAID (naproxen 500mg x1 or indomethacin 50mg x3) vs. oral glucocorticoids (prednisolone 30mg or 35mg x1) (N =2) NSAID (indomethacin 50mg x4) vs. ACTH (40 IU x1) (N = 1) NSAID (indomethacin 50mg x3 then 25mg x3) vs. rilonacept (320mg) (N=1) NSAID (indomethacin 25mg x3) vs. Acupuncture + IR	NSAID vs. placebo: More participants reported >50% pain relief after 24 hrs with NSAID; No difference in proportion with >50% improvement in joint swelling; No AE's with NSAIDs, but some with placebo. NSAID vs. COXIB: similar pain, swelling and global improvement but fewer AE's with COXIB; fewer withdrawals due to AE's in COXIB. Lower total AE's with COXIB. NSAID vs. glucocorticoids: No difference in pain reduction, function, or AE's.	10/10

Author/Year/ Funding	End Date of Search	# of Included Studies	# of Included Patients/Patient Characteristics Included	Setting(s)	Outcomes	Doses	Results	AMSTAR
Khanna, et. al, 2014[47]; NSAIDs, COX-2 inhibitors, ACTH, IL-1, Simiao Pill, topical ice. /Funding: ACR Gout Guidelines Grant	5/5/2013	30 RCTs (28 active comparator studies; 2 with a placebo-controlled group)	Number of patients not reported; pooled mean age 54.14 (SD = 11.94); 89.7% male	NR	Pain (multiple measures)	NR	Oral colchicine is effective for acute gout. Corticosteroids and possibly ACTH potentially good alternative in subjects with contraindications to NSAIDs or colchicine therapy. IL-1B promising for acute gout that is refractory or has contraindications to conventional therapy.	6/9
Echteld et al., 2014[50]/Colchicine/Funding = Cochrane Musculoskeletal Group, Australia	4/30/2014	2 RCTs	N = 124/Age 18+ with diagnosis of acute gout (i.e. author defined or MSU crystals in joint aspirate or ACR criteria or Rome criteria or New York criteria)	Hospital and Outpatient	Proportion of participants with >50% decrease in pain; Withdrawal due to AE's; Reduction of inflammation; Function of target joint; Patient global assessment of treatment success; HRQoL; Total AE's, serious AE's, and type	0.5mg colchicine every two hours; 4.8mg colchicine over 6 hours	Low-quality evidence that high dose colchicine relieves pain greater than 50%; Total AE's higher in high-dose colchicine vs. placebo; Low-quality evidence that high-dose colchicine provides 50% or greater decrease in	10/10

Author/Year/ Funding	End Date of Search	# of Included Studies	# of Included Patients/Patient Characteristics Included	Setting(s)	Outcomes	Doses	Results	AMSTAR
					of AE's.		joint inflammation score. Low-quality evidence that low-dose colchicine is more efficacious than placebo with respect to greater than 50% decrease in pain; there are no additional AE's for colchicine vs placebo. High-dose and low-dose colchicine approximately equal in providing greater than 50% pain relief; More AE's with high-dose colchicine vs. low-dose colchicine.	

Author/Year/ Funding	End Date of Search	# of Included Studies	# of Included Patients/Patient Characteristics Included	Setting(s)	Outcomes	Doses	Results	AMSTAR
Terkeltaub, 2008[49]; Colchicine/VA Research Service, NIH, AR Scientific, Regeneron, ARDEA, Novartis, Pfizer, TAP, Savient, BioCryst	Jul-08	2 RCTs	86/characteristics not reported	Not reported	Frequency and severity of gouty arthritis flares; Proportion of participants reporting >50% reduction in pain;	0.6mg twice daily vs. placebo (N=1) 1mg, then 0.5mg every 2 hours until a complete response or toxicity developed vs. placebo (N=1)	Addition of colchicine as a prophylactic in allopurinol treatment for urate lowering therapy, reduced the frequency and severity of gouty arthritis flares. Colchicine also effective in reducing the pain associated with gout flares.	1/9
Daoussis et. al., 2014[46]/Funding: Not reported	Not reported	5 (2 RCTs, 3 retrospective chart reviews)	n=266/characteristics not reported	Not reported	Time to complete resolution; time to pain relief	40 IU ACTH single dose (N=2) 100 IU ACTH single dose (N=1) 40 or 80 IU ACTH tid, gradual tapering (N=2)	ACTH is effective in treating acute gout and can be used in patients with multiple comorbidities due to its excellent safety profile.	2/9

Author/Year/ Funding	End Date of Search	# of Included Studies	# of Included Patients/Patient Characteristics Included	Setting(s)	Outcomes	Doses	Results	AMSTAR
Wechalekar,2014[51] Intraarticular Glucocorticoids, Colchicine, NSAIDs, IL-1	9/30/2011	26 RCTs	N = NR/Adults 18+ with acute gout defined by study authors, presence of MSU crystals, or fulfilling the ACR, Rome, or New York criteria	NR	Pain; withdrawal due to AE's or SAE's; inflammation, patient global assessment, function of target joint, HRQoL, number of participants with AE's.	See Table 1 in study	Systemic GC as effective as NSAID but safer (moderate-quality, N=3); High and Low-dose colchicine more effective than placebo; Low-dose colchicine no safer than placebo but safer than high-dose colchicine (low-quality; N=1); No difference between NSAID and placebo in terms of pain (low-quality; N=1)	7/9
Wechalekar 2013[43] Intra-articular glucocorticoids/ Funding: No sources supplied	10/16/2012	0	N/A	N/A	Pain; proportion of participant withdrawals due to AE's; inflammation; function; patient global assessment of treatment success; quality of life; proportion of participants with serious AE's	N/A	No trials were identified that evaluated the efficacy and safety of intra-articular glucocorticoids for acute gout.	7/7

Table 4. Randomized controlled trials of pharmacologic therapies for acute gout not included in existing systematic reviews

Author/ Year	Objective	Population, Sample size	Diagnosis of gout	Intervention	Comparison	Outcomes	Timing	Results	Cochrane ROB
Karimzadeh 2006[55]	Efficacy of colchicine prophylaxis in prevention of acute gout attacks for patients undergoing urate lowering therapy	N = 190, patients with gouty arthritis, at least one year after diagnosis, and on long-term ULT presenting to hospital rheumatology department	Unclear	Allopurinol + Colchicine for: 3-6 months (Group 1) vs. 7-9 months (Group 2) vs. 10-12 months (Group 3)	Allopurinol + Colchicine over time	Probability of recurrence of gout attacks; sUA levels	6 months, 12 months	Probability of recurrence at 6 months: 46% (3-6mos), 11%(7-9 mos), 6% (10-12 mos). Probability of recurrence at 12 months: 54% (3-6 mos), 27.5% (7-9 mos), 23% (10-12 mos). No difference in sUA levels.	1. Sequence: Low 2. Allocation concealment: High 3a. Blinding participants: High 3b. Blinding care providers: High 3c. Blinding outcome assessors: High 4a. Follow-up less than 20%: Low 4b. Loss to follow-up missing data explained: High 4c. Only those who completed the treatment program 5. Outcome reporting: Low 6. Findings reported as % who responded: High

Author/ Year	Objective	Population, Sample size	Diagnosis of gout	Intervention	Comparison	Outcomes	Timing	Results	Cochrane ROB
Zhang 2014[54]	Comparing NSAIDs vs. IM GC in acute gout treatment	N = 60, patients with an acute gout attack within 24 hrs.	ACR guidelines	Betamethasone (glucocorticoid) 7mg IM once vs. Diclofenac Sodium 75mg b.i.d. for 7 days	Glucocorticoid vs. NSAID	Pain intensity, tenderness, swelling, and global assessment of response to therapy, sUA levels	7 days	In terms of change in pain intensity from baseline, betamethasone preferred on Day 3 and comparable to diclofenac sodium on Day 7. (See Table 1) Fewer AE's for betamethasone (see Table 3) No significant differences in sUA levels.	1. Sequence: Low 2. Allocation concealment: High 3a. Blinding participants: Low 3b. Blinding care providers: High 3c. Blinding outcome assessors: High 4a. Follow-up less than 20%: Low 4b. Loss to follow-up missing data explained: Low 4c. All participants randomized to particular groups 5. Outcome reporting: Low 6. Findings reported as % who responded: Low

Author/ Year	Objective	Population, Sample size	Diagnosis of gout	Intervention	Comparison	Outcomes	Timing	Results	Cochrane ROB
Li 2013[53]	COX-2 vs. NSAIDs in treating acute gout	N=178, with an acute gouty attack (<48 hours)	ACR guidelines	Etoricoxib (120mg/day) vs. Indomethacin (75mg/day x 2)	COX-2 vs. NSAID	Self-assessed pain in affected joint, tenderness and swelling, global assessment of response to therapy, patients discontinuing treatment, AE	5 days	No difference between etoricoxib and indomethacin in terms of pain in affected joint. Mean change difference from baseline to days 2- 5 was 0.03 (95% *CI* – 0.19 to 0.25; *P*=0.6364). No significant difference in adverse events. Absolute number of AE's: Etoricoxib (n=31) vs. Indomethacin (n=34).	1. Sequence: Low 2. Allocation concealment: Unclear 3a. Blinding participants: Low 3b. Blinding care providers: Low 3c. Blinding outcome assessors: Low 4a. Follow-up less than 20%: Low 4b. Loss to follow-up missing data explained: Low 4c. All participants randomized to particular groups 5. Outcome reporting: Low 6. Findings reported as % who responded: High

Table 5. Randomized controlled trials of NSAID versus NSAID for treatment of acute gout

Author, Year	Sample Size	NSAID 1	Dose 1	NSAID 2	Dose 2	Statistically or Clinically Important Differences in Effectiveness
Douglas et al., 1970[67]	25	Flufenamic acid	800mg/d x 4 d, then 400mg/d	Phenylbutazone	800mg/d x 4 d, then 400mg/d	No
Siegmeth et al., 1976[83]	46	Ketoprofen	50mg/BID	Phenylbutazone	300mg/BID	No
Ruotsi et al., 1978[76]	18	Proquazone	300mg/TID, then 300mg/QD	Indomethacin	50mg/TID, then 50mg/QD	No
Weiner et al., 1979[87]	30	Fenoprofen	3.6g day1, then 3.0g day 2-4	Phenylbutazone	700mg day1, then 400mg day 2-4	No
Eberl et al., 1983[68]	20	Meclofenamate	800mg/day, then 100mg/TID	Indomethacin	200mg/day, then 50mg/TID	No
Butler et al., 1985[64]	33	Flurbiprofen	400mg/d x 2d, 200mg/d	Phenylbutazone	800mg/d x 2d, 400mg/day	No
Lomen et al., 1986[71]	29	Flurbiprofen	400mg/d x 1 day, then 200mg/d	Indomethacin	200mg/day x 1 day, then 100mg/day	No
Altman et al., 1988[61]	59	Ketoprofen	100mg/TID	Indomethacin	50mg/TID	No
Lederman et al., 1990[70]	60	Etodolac	300mg/BID	Naproxen	500mg/TID	No
Maccagno et al., 1991[72]	61	Etodolac	300mg/BID	Naproxen	500mg/BID	No
Shrestha et al., 1995[81]	20	Ketorolac	60mg/once	Indomethacin	50mg/once	No
Schumacher et al., 2002[78]	150	Etoricoxib	120mg/QD x 8d	Indomethacin	50mg/TID x 8d	No

Author, Year	Sample Size	NSAID 1	Dose 1	NSAID 2	Dose 2	Statistically or Clinically Important Differences in Effectiveness
Cheng et al., 2004[65]	62	Rofecoxib	50mg	Diclofenac	150mg	Rofecoxib equivalent to diclofenac Rofecoxib superior to meloxicam Meloxicam equivalent to diclofenac
				NSAID 3: Meloxicam	15mg	
Rubin et al., 2004[75]	189	Etoricoxib	120mg/QD	Indomethacin	50mg/TID	No
Schumacher et al., 2012[79]	400	Celecoxib	50mg/BID, 200mg/ BID, 400mg/BID	Indomethacin	50mg/TID	High dose celecoxib equivalent to indomethacin Low dose celecoxib inferior to indomethacin
Li et al., 2013[53]	78	Etoricoxib	120mg/d	Indomethacin	75mg/BID	No

Key Question 2: Dietary and Lifestyle Management of Gout

a. In adults with gout, what are the benefits and harms of different dietary therapies and life style measures on intermediate (serum and/or urine UA levels) and final health outcomes (including recurrence of gout episodes and progression [e.g., development of tophi])?
b. Does effectiveness and comparative effectiveness of dietary modification differ according to disease severity (including presence of tophi and baseline serum UA), underlying mechanisms of hyperuricemia, or baseline demographic and co-morbid characteristics?

Key Points

- The SoE from RCTs that assess symptomatic outcomes is insufficient to support a role for specific dietary changes (including reducing intakes of dietary purines, protein, or alcohol; increasing intakes of cherries, modified milk products, or supplemental vitamin C; or achieving weight loss) in gout management.
- The SoE is insufficient to support a role for gout-specific dietary advice (counseling about reducing red meat intake; avoiding offal, shellfish, and yeast-rich foods and beverages; and including low fat dairy products, vegetables, and cherries) compared with nonspecific dietary advice (counseling about the importance of weight loss and reduced alcohol intake) for reducing serum urate levels in patients with gout.
- The SoE is insufficient to support or refute the effectiveness of Traditional Chinese Medicine (TCM; including herbs and acupuncture) on symptomatic outcomes.

Description of Included Studies

For this KQ, we include five SRs,[47, 93-96] that report findings for Traditional Chinese Medicine practices. The studies included in these SRs are shown in Table 6, and the SRs are further described in Table 9.

We identified six RCTs and three prospective observational studies (described in six publications) that met our inclusion criteria and that examined dietary, lifestyle, and TCM interventions in gout management.[23, 97-107] These studies are described in Tables 7 and 8.

One RCT assessed the effects of supplementing the diet with three different enriched skim milk products on frequency of gout flares among 120 individuals who were experiencing frequent gout flares.[102] Another RCT assessed the efficacy of vitamin C supplementation in lowering serum urate in 40 patients with established gout.[104] Two RCTs[103, 106] assessed the effects of dietary advice on gout management. These studies, published in 2010 and 2014, enrolled adult male patients with history of gouty arthritis. The 2010 study,[103] which was in Chinese, enrolled sixty-seven male patients with gout, average age of 61 years, history of overweight and at least one gouty attack during the six months before enrollment. The 2014 study[106] enrolled 30 adult patients with a history of gout, receiving an appropriate and stable dose of urate lowering therapy (ULT).

Three SRs examined the efficacy of Traditional Chinese Medicine (TCM) in the management of gout while one examined the efficacy of acupuncture and one examined the efficacy of

moxibustion for rheumatic conditions. The AMSTAR ratings of these 5 SRs ranged from moderate to good quality. A single RCT[105] evaluated the efficacy of TCM in gout management. The study was conducted in 2010 and enrolled male patients with acute gouty arthritis and an average age of 48.[105]

Table 6. Randomized controlled trials included in systematic reviews of Traditional Chinese Medicine Interventions

	Systematic Reviews				
RCTs	**Li et al., 2013[95]**	**Zhou et al. 2013[96]**	**Lee et al. 2013[94]**	**Khanna et al. 2014[47]**	**Choi et al. 2011[93]**
Zhou 201288			X		
Chou 199566				X	
Shi 200880	X			X	
Schlesinger 200277				X	
Feng, 2003108					X

Detailed Synthesis

Interventions Involving Dietary Factors

Original Randomized Controlled Trials of Dietary Interventions

A trial[102] by Dalbeth and colleagues with low to moderate risk of bias assessed whether skim milk powder (SMP) enriched with glycomacropeptide (GMP) and G600 milk fat extract, non-enriched SMP, or lactose powder significantly reduced the frequency of gout attacks (flares) over a three-month study period. The frequency of gout attacks (flares) decreased from baseline in all three groups, however there was no significant difference among the three arms in terms of the change in the number of gout attacks (flares) or in adverse events.

An RCT of 40 adult gout patients by Stamp and colleagues[104] with moderate to high risk of bias compared the effects of vitamin C supplementation to that of allopurinol.[104] The study found that the reduction in serum urate level over 8 weeks was significantly less in those patients receiving vitamin C than in those who started or increased their dose of allopurinol (mean reduction 0.014 mmoles/liter [0.23mg/dl] versus 0.118 mmoles /liter [1.9mg/dl]; $P < 0.001$). They concluded that when administered as monotherapy or in combination with allopurinol, the uric acid lowering effect of a modest dose of vitamin C seems to be small in patients with gout.[104]

We also identified two RCTs[103, 106] that assessed the effects of dietary advice or a specific diet on gout (Table 7).

A 2014 RCT by Holland and McGill [106] compared the effects of comprehensive gout-specific dietary advice with basic advice on serum urate in gout patients. The study divided 30 gout patients (on ULT, not further specified) into an intervention group (n=14) that received comprehensive dietary advice focused on gout management, based on the British Society of Rheumatology Guidelines and a control group (N=15) that received basic advice regarding the importance of compliance with therapy and the benefit of weight loss. Two educational sessions

were provided: once at baseline and once at 3 months. The study found a significant increase in knowledge and an increase in self-reported dietary modification among the group that received gout-specific advice but no differences in serum urate between the two groups at the end of 6 months ($p>0.05$).[106] The study did not implement a clinical measure of dietary compliance (including weight loss), and self-reported compliance was extremely low. The study had a high risk of bias.

A 2012 RCT[103] investigated the effects of adjusted proportional macronutrient intake on serum urate and gout attacks in overweight patients with gout. Sixty one gout patients were randomized to one of two isocaloric (1500 cal/d) diets: high protein (40% complex CHO, 30% protein, 30% unsaturated fat), or the control low purine diet (60% CHO, 10% protein, 30% fat; purine <150mg/d). The study found that frequency of gouty attacks (17 vs 28, P=0.000) and serum urate levels(420.25±36.78 vs 466.81±41.97 μmol/L, P=0.000] were significantly reduced in the high protein group compared with the low purine group.[103] This study also had a high risk of bias.

Original Prospective Observational Studies of Dietary Factors and Risk for Gout Flare

The Boston University (BU) Online Gout Study is an internet-based prospective observational (case-crossover) study aimed at assessing the role of dietary factors in the risk for gout flare. Over 600 patients with physician-diagnosed gout (verified by two rheumatologists using ACR criteria) and at least one gout flare in the preceding year enrolled online. Over a one-year period, patients were instructed to complete 48-hour dietary recall surveys prior to gout flares and during several two-day periods of no gout activity. Use of pharmacological treatments, including gout medications, was also noted.

Zhang and colleagues reported that compared with the lowest quintile of total purine intake over a 2-day period, the OR for recurrent gout attacks were 1.17, 1.38, 2.21 and 4.76, respectively, by increasing quintile (p for trend <0.001).[99] For purines from animal sources, the corresponding OR were 1.42, 1.34, 1.77 and 2.41 for increasing quintiles (p for trend <0.001), and for purines from plant sources, the OR was 1.12, 0.99, 1.32 and 1.39 (p=0.04), respectively. Subgroup analysis showed no effect of sex, use of alcohol, diuretics, allopurinol, NSAIDs and colchicine.

In a subsequent publication, the researchers also reported that cherry intake over a 2-day period was associated with a 35% lower risk of gout attacks compared with no cherry intake (multivariate OR 0.65 [95% CI 0.50–0.85]).[100] Cherry extract intake showed a similar inverse association (multivariate OR 0.55 [95% CI 0.30–0.98]). Subgroup analysis showed that these findings were not affected by differences in sex, age, weight status, purine intake, alcohol use, diuretic use or use of gout medications. However, when the effect of cherry intake was considered in combination with allopurinol use, the risk of gout attacks was 75% lower than during periods without either cherry juice or allopurinol (OR 0.25, 95% CI 0.15, 0.42).

Early in the study, the researchers analyzed the association between alcohol intake and risk for gout flare among an initial group of 179 patients.[101] Compared with no alcohol consumption, the OR for recurrent gout attacks were 1.1, 0.9, 2.0, and 2.5 for 1 to 2, 3 to 4, 5 to 6, and 7 or more drinks consumed over the 2-day period, respectively (P=.005). A dose-response relationship of risk of gout attacks was more evident for alcohol consumed during the prior 24 hours. An increased risk of recurrent gout attacks was found for each type of alcoholic beverage consumed, although the sample size precluded assessing the statistical significance of this observation. A follow-up study with a larger patient population also found a significant dose response relationship between the amount of alcohol consumed and the risk for recurrent flare ($p<0.001$ for trend).[98] The

risk for recurrent gout attack was 1.36 (95% CI 1.00, 1.88) for >1-2 drinks per day and 1.51 (95% CI 1.09, 2.09) for >2-4 drinks in the prior 24 hours, compared with no alcohol. This study found no difference in the risk by the type of alcohol consumed (beer, wine, or hard liquor).

Two studies have assessed the association between weight loss and serum urate levels in men with gout. Zhu and colleagues assessed the association between weight loss and serum urate levels among the men enrolled in the Multiple Risk Factor Intervention Trial (MRFIT).[23] Compared with men who did not lose weight, those with weight loss in the three higher quartiles showed a significant increase in the OR of achieving the target serum urate level of ≤60μmol/L ($p<0.001$). The increase in the odds of achieving the target serum urate did not differ between men with gout and those without gout (the serum urate level changes for the second, third, and fourth quartiles were 7, 19 and 37 mmol/L). Dalbeth and colleagues assessed the association between bariatric surgery-induced weight loss and serum urate levels among obese individuals with Type II diabetes and gout. At the beginning of the study, 83 percent of participants had serum urate levels above the therapeutic target (≥.36mmol/L); one year after surgery, 33 percent had urate levels above the target ($p=0.031$).[97]

Traditional Chinese Medicine (TCM)

TCM encompasses herbal medicine, acupuncture, massage, exercise, and dietary therapies. For this review, we limited the modalities we considered to acupuncture (moxibustion) and herbal therapies. We identified five SRs that evaluated the efficacy of TCM practices in gout management: three compared multiple TCM modalities to conventional medicine (Table 9), one evaluated the efficacy of acupuncture compared with conventional medicine in gout management, and one evaluated moxibustion for the treatment of rheumatic conditions.[95 47, 93, 94, 96] The TCM evaluated included a wide range of delivery methods (including decoction, granule, capsule, and pill) and multiple mixtures of herbs (up to 23 in one SR), whose extracts have been found in some cases to contain active ingredients such as colchicine.[95] In aggregate, the SRs of TCM included evidence from 86 RCTs. [47, 94-96] Of these RCTs, 58 assessed the efficacy of TCM as ULT compared with conventional therapies, two assessed the recurrence of attacks (flares), 13 assessed pain reduction, 12 assessed reduction in inflammation/joint swelling, and 44 assessed adverse reactions associated with TCM.

Two SRs[95, 96] that reported pooled estimates found conflicting evidence on the efficacy of TCM in reducing serum urate level in gout management. Li (2013)[95] concluded that the mean serum urate level in the TCM intervention groups was 50.1 micromol/L lower than the mean serum urate level after treatment in the control groups, which had conventional medicine (MD −50.10 [−54.37, −45.83]). The SR was of good quality while the quality of evidence of pooled estimates was judged to be moderate.[95] However, results from a meta-analysis by Zhou et al 2013[96] found no significant difference in clinical efficacy between Chinese herbal decoctions and traditional Western medicine as measured by serum urate (standardized mean difference (SMD):0.35, 95% CI): 0.03 -0.67) and overall clinical response (relative risk (RR): 1.05, 95% CI: 1.01-1.10) among patients experiencing acute gout flares. The SR was moderate in quality. In addition, the SR of Khanna (2014)[47] describes an RCT[66] of 40 adult gout patients that found no significant reduction in serum urate level in a group given a Chinese herbal formulation compared with a group given indomethacin and allopurinol.

Two SRs addressed the efficacy of TCM for pain relief for gout management.[47, 95] A trial[66] described by Khanna et al (2014)[47] found no significant improvement in pain score for treatment with DDNT compared with indomethacin. Li et al 2013[95] also concluded from the results of their

meta-analysis of 12 studies that the evidence was insufficient to show a statistically significant effect of TCM compared with conventional medications for pain relief (mean difference [MD], −0.03; 95 % confidence interval [CI],-0.06, 0.00), but TCM combined with conventional medicines may have better effectiveness (MD, −0.33; 95 %CI, −0.59, −0.07) than conventional medications alone.

Evidence on the efficacy of TCM in reducing inflammation and joint swelling is also conflicting. Li et al 2013[95] conclude from their pooled analysis of 10 RCTs that the mean difference in inflammation from joint swelling after treatment in the intervention groups (TCM) was 0.14 lower (0.03 to 0.25 lower) than the mean inflammation from joint swelling after treatment in the control (conventional medicine) groups (MD −0.07 [−0.11,−0.02]). The quality of evidence (GRADE) from the pooled analysis was judged to be moderate. In addition, Khanna et al (2014)[47] describe a study by Shi et al (2008)[80] that finds Simiao pill more efficacious than Indomethacin at Day 7 in reducing joint swelling and tenderness. However another study[66] described by them found no significant improvement in the number of painful and swollen joints with an herbal formulation (DGNT) when compared with indomethacin. Li (2013)[95] also found no evidence showing that TCM prevents recurrence of gout attacks (flares).

Li et al (2013)[95] found evidence suggesting that TCM is associated with fewer adverse effects than are conventional therapies [risk ratio (RR), 0.11; 95% CI, 0.08 to 0.15]. Zhou et al (2013)[96] also described evidence suggesting that a Chinese herbal decoction was associated with significantly fewer adverse drug reactions than was traditional Western medicine (RR: 0.06, 95% CI: 0.03 to 0.13). We identified one systematic review that evaluated the efficacy of acupuncture in comparison with conventional therapy for gout management.[94] Results from pooled analysis suggest that acupuncture therapy is more effective in reducing serum urate level (MD = 30.37; 95% CI 4.28, 56.47; P<0.00001) and pain (MD 2.23; 95% CI 1.39 - 3.08; P<0.0001) than is conventional therapy. However, two out of the eight trials (120 patients) reported a worse effect of acupuncture than the control treatment on uric acid.[94] The quality of the systematic review was moderate.

We identified one SR that evaluated the efficacy of moxibustion in comparison with conventional therapies for the treatment of pain and inflammation associated with rheumatic conditions.[93] Two of the included studies enrolled gout patients; however only one compared moxibustion with a medication approved for use in the US, allopurinol. Patients treated with ginger moxibustion showed an increased response rate compared with patients treated with allopurinol (100 percent response rate vs. 75 percent response rate, respectively).[108]

We identified two new RCTs that evaluated the efficacy of TCM in gout management (see Table 8). Zhang (2010),[105]in a study that we judged had high risk of bias, investigated the "cure rate" in a group that received blood-letting cupping plus TCM compared with a control group that received Diclofenac Sodium Enteric-coated Tablets. They found that the "cure rate" (measured by resolved joint swelling, reduced pain, and normal or decreased blood uric acid) was higher in the treatment group (61 percent) than in the control group (58 percent), however the difference was not significant at the 5 percent level.

Wang et al (2014),[107] in a study of 176 outpatients with newly diagnosed acute gouty arthritis, compared recurrence rate and adverse events between the treatment group, which received Chuanhu anti-gout mixture and the control group, which received colchicine. The treatment group had a significantly lower overall recurrence rate, fewer adverse events, and greater changes in serum uric acid compared with the control group. The authors conclude that their findings suggest

that Chuanhu anti-gout mixture is non-inferior to colchicine and can be considered an alternative choice for the treatment of acute gouty arthritis.

Table 7. Studies assessing dietary factors and treatment of gout

Author, year, Location, Design	Participants, N, Inclusion/Exclusion Criteria	Interventions/exposures/ Controls	Outcomes	Findings	RoB
Holland, 2014[106] Australia RCT	29 adults with hx of gout (age range 38-80; median 61) with stable gout on ULT, serum urate<0.36 mmol/L	Baseline knowledge testing questionnaires Intervention: British Society for Rheumatology advice on dietary gout management: (reducing red meat; avoiding offal, shellfish, yeast extract; adding low fat dairy foods, coffee, vegetables, and cherries at baseline and 3 months Control: baseline advice on weight loss, exercise, drug therapy compliance, reducing alcohol intake, and target serum urate	Serum urate at 3 and 6 months, knowledge, dietary modifications	At 6 months, intervention group had significantly improved knowledge and self-reported dietary modification compared with baseline and controls but no difference in serum urate	1. Sequence: Low 2. Allocation concealment: High 3a. Blinding participants: Low 3b. Blinding care providers: High 3c. Blinding outcome assessors: Unclear 4a. Follow-up less than 20%: Low 4b. Loss to follow-up missing data explained: Low 4c. Unclear if all participants randomized to particular groups 5. Outcome reporting: Low 6. Findings reported as % who responded: High

Author, year, Location, Design	Participants, N, Inclusion/Exclusion Criteria	Interventions/exposures/ Controls	Outcomes	Findings	RoB
Zeng, 2012[103] China RCT	61 overweight patients with gout (mean age 61.46±14.52 for intervention group) Inclusion: at least 1 gout attack in prior 6 months	Intervention: High protein diet 40% complex CHO, 30% protein, 30% unsaturated fat Control: Low purine diet contained 60% CHO, 10% protein, 30% fat (purine <150mg/d) Both diets were isocaloric (1500 kcal/d)	Weight, uric acid, serum lipids, # gout attacks at 6 months	High protein group lost significantly more weight than the low purine group (p=0.043); and had significantly lower serum UA (420±37 vs. 467±42 umol/L, p=0.000) and fewer gout attacks (48.48% decrease vs. 22.22% decrease, p=0.000); triglycerides decreased and HDL increased in the high protein group.	1. Sequence: Low 2. Allocation concealment: High 3a. Blinding participants: Unclear 3b. Blinding care providers: Unclear 3c. Blinding outcome assessors: Unclear 4a. Follow-up less than 20%: Low 4b. Loss to follow-up missing data explained: Low 4c. Only those who completed the treatment regimen 5. Outcome reporting: Low 6. Findings reported as % who responded: High

Author, year, Location, Design	Participants, N, Inclusion/Exclusion Criteria	Interventions/exposures/ Controls	Outcomes	Findings	RoB
Stamp, 2013[104] New Zealand RCT	40 patients (90% male; mean age Vitamin C: 61.2 , no Vitamin C: 55.0; mean BMI 31) with ACR-dx gout (and SU>0.36 mmol/L), 20 taking allopurinol and 20 not taking allopurinol; use of OTC vitamins excluded	Intervention: patients already taking allopurinol were randomized to receive an increased dose or to begin taking Vitamin C (500 mg/d) Patients not taking allopurinol randomized to receive allopurinol (up to 100mg/d to a target sUA <0.36) or vitamin C; open label, 8 weeks	Baseline, 4-week, and 8-week serum urate, ascorbate, and oxypurinol	Vitamin C resulted in a significant increase in serum ascorbate but a significantly smaller decrease in serum urate (0.014 mmol/L) than did allopurinol (either initiating tx or increasing dose)(0.118, p<0.001)	1. Sequence: Low 2. Allocation concealment: High 3a. Blinding participants: High 3b. Blinding care providers: High 3c. Blinding outcome assessors: Low 4a. Follow-up less than 20%: Low 4b. Loss to follow-up missing data explained: Low 4c. All participants randomized to particular groups 5. Outcome reporting: Low 6. Findings reported as % who responded: High

Author, year, Location, Design	Participants, N, Inclusion/Exclusion Criteria	Interventions/exposures/ Controls	Outcomes	Findings	RoB
Dalbeth, 2012[102] New Zealand RCT	120 patients (91% male; mean age 56) with recurrent gout flares (mean self-reported flares in preceding 4 months: 3.9±2.7-5.1±9.6)	Active intervention 1: Skim milk powder (SMP) Active intervention 2: SMP enriched with glycomacropeptide and G600 milk fat (SMP/GMP/G600) Control: Lactose	Recurrence of gout attacks, as defined by pain at rest of >3 on a 10-point scale and patient self-reported flare over 3 months; urinary uric acid	Gout flare frequency decrease in all 3 groups at 3 months; Decrease was significantly greater in the (SMP/GMP/G600) group, along with fractional excretion of uric acid, pain, and a trend to greater improvement in tender joint count.	1. Sequence: Low 2. Allocation concealment: Low 3a. Blinding participants: Low 3b. Blinding care providers: Low 3c. Blinding outcome assessors: Low 4a. Follow-up less than 20%: Low 4b. Loss to follow-up missing data explained: Low 4c. All participants randomized to particular groups 5. Outcome reporting: Low 6. Findings reported as % who responded: High
Zhang, 2006[101] US BU Online Gout Study Case-crossover	179 patients (80% male; median age 52) with gout according to ACR criteria (median duration of disease 8 years; median duration of current flare 2 days). Patients completed 48-hour diet and lifestyle recall questionnaires during gout attacks	Exposure: alcoholic drinks	Risk for recurrent gout attacks	Compared with no alcohol consumption, odds ratios for recurrent gout attacks were 1.1, 0.9, 2.0, and 2.5 for 1 to 2, 3 to 4, 5 to 6, and 7 or more drinks consumed over the 2-day period, respectively (P<.005)	Not rated

Author, year, Location, Design	Participants, N, Inclusion/Exclusion Criteria	Interventions/exposures/ Controls	Outcomes	Findings	RoB
Zhang, 2012[100] US BU Online Gout Study Case-crossover	663 U.S. patients with MD-diagnosed gout (confirmed in medical records by two rheumatologists via ACR criteria),18 years and older (mean age 54, 78% male), having had a gout attack within the past 12 months, who completed 48-hour diet and lifestyle recall questionnaires during gout attacks and control periods free of gout symptoms	Exposure: Cherries and cherry juice, ascertained through 48-hour dietary recall	Risk for recurrent gout attacks	Cherry intake over a 2-day period was associated with a 35% lower risk of gout attacks compared with no intake (multivariate OR 0.65, 95% CI 0.50, 0.85). Cherry extract showed similar association (multivariate OR 0.55, 95% CI 0.30, 0.98). Association was unaffected by sex, obesity status, purine intake, alcohol use, diuretic use, and use of anti-gout medications; Allopurinol use magnified the association.	Not rated

Author, year, Location, Design	Participants, N, Inclusion/Exclusion Criteria	Interventions/exposures/ Controls	Outcomes	Findings	RoB
Zhang, 2012[99] US BU Online Gout Study Case crossover	See Zhang 2012 above; 663 patients, of whom 554 had crystal-proven gout	Exposure to purine-rich foods	Risk for recurrent attacks	1,247 gout attacks verified. Compared with the lowest quintile of total purine intake over a 2-day period, OR of recurrent gout attacks were 1.17, 1.38, 2.21 and 4.76, respectively, with each increasing quintile (p for trend <0.001). The corresponding OR were 1.42, 1.34, 1.77 and 2.41 for increasing quintiles of purine intake from animal sources (p for trend <0.001), and 1.12, 0.99, 1.32 and 1.39 from plant sources (p=0.04), respectively. The effect of purine intake persisted across subgroups by sex, use of alcohol, diuretics, allopurinol, NSAIDs and colchicine	Not rated
Neogi, 2014[98] BU Online Gout Study Case-crossover	724 participants with gout (78% male, mean age 54 years) who reported at least 1 gout attack during a 1-year follow-up	Exposure: alcohol quantity and type during 24 hours prior to a gout attack	Risk for recurrent gout attacks	Amount of alcohol consumed was significantly associated with risk for recurrent gout attacks (p<0.001 for trend; >1-2 drinks: RR 1.36 (95% CI 1, 1.88); >2-4 drinks: RR 1.51, (1.09, 2.09) compared with no alcohol. Type of alcohol was not a factor.	Not rated

Author, year, Location, Design	Participants, N, Inclusion/Exclusion Criteria	Interventions/exposures/ Controls	Outcomes	Findings	RoB
Zhu, 2010[23] US MRFIT Post hoc analysis of RCT	12,379 males (35-57 years of age at baseline) at increased CVD risk (number of participants with gout not specified) enrolled in minimum 1-year dietary trial to reduce risk factors	Intervention: diet to achieve weight loss	Odds for achievement of target serum uric acid levels	A 1-kg weight loss was associated with 11% increased odds of achieving the therapeutic Goal, independent of any other factors. For men with gout, weight losses of >10 kg, 5-9.9kg, and 1-4.9kg were associated with OR of 3.19 (1.99, 5.09), 2.33 (1.75, 3.11), and 1.53 (1.24, 1.89) of achieving the target urate compared with men who did not lose weight.	Not rated
Dalbeth, 2014[97] Australia Prospective weight loss study	60 obese individuals with Type II diabetes (12 with gout, mean age 49(8) 42% female)	One year of non-surgical weight loss and bariatric surgery	Likelihood of achieving target serum urate at one-year post bariatric surgery	In participants with gout, mean (SD) weight reduced from 134.3 (24.3) kg at baseline visit to 100.3 (16.3) kg at the final study visit ($p<0.0001$). SU above therapeutic target levels ($\geq$0.36 mmol/L) were present in 10/12 (83%) at baseline and 4/12 (33%) 1 year after surgery ($p=0.031$).	Not rated

Table 8. Randomized controlled trials of Traditional Chinese Medicine therapies for acute gout not included in existing systematic reviews

Author/Year	Population, Sample Size	Intervention	Outcomes	Timing	Results	Cochrane ROB
Zhang, 2010[105]	67 cases of acute gouty arthritis; male; aged 32-71 with an average of 48.	blood-letting cupping plus TCM (treatment group) vs. Diclofenac Sodium Enteric-coated Tablets(control group) (3 times daily for 3–7 days)	"Cure rate"" (resolved joint swelling, reduced pain, and normal or decreased blood uric acid)	1 week	"Cure rate" (resolved joint swelling, reduced pain, and normal or decreased blood uric acid) was 61% in treatment group compared with 58% in the control group. However the difference was not significant at the 5% level.	1. Sequence: Low 2. Allocation concealment: High 3a. Blinding participants: High 3b. Blinding care providers: High 3c. Blinding outcome assessors: High 4a. Follow-up less than 20%: Low 4b. Loss to follow-up missing data explained: Low 4c. All participants randomized to particular groups 5. Outcome reporting: Low 6. Findings reported as % who responded: Low
Wang et al 2014[107]	176 outpatient individuals (aged > 18 years; 166 men) with newly diagnosed acute gouty arthritis	Patients were randomized to either Chuanhu anti-gout mixture 250 ml orally daily (n=88) or Colchicine mimetic agent) (n=88).	Recurrence rates; changes in white blood cells and C-reactive protein; adverse events	12 weeks	The overall recurrence rates in the Chuanhu anti-gout mixture group (CH group) and the Colchicine group (Col group) were 12.50% vs 14.77% (difference -2.22%, 95% CI:10.78%-6.23%) respectively, suggesting that Chuanhu anti-gout mixture is not inferior to colchicine. There were less adverse events in the CH group compared with the Col group (2.27% vs 28.41%, 95% CI: 0.01-0.26). Changes in blood uric acid in the CH group were significantly larger compared with those in the Col group (P<0.05).	1. Sequence: Low 2. Allocation concealment: Unclear 3a. Blinding participants: Low 3b. Blinding care providers: Low 3c. Blinding outcome assessors: Unclear 4a. Follow-up less than 20%: Low 4b. Loss to follow-up missing data explained: Low 4c. All participants randomized to particular groups 5. Outcome reporting: Low 6. Findings reported as % who responded: Low

Table 9. Systematic reviews of Traditional Chinese Medicine interventions for acute gout treatment

Author/Year/ Funding	Search End date	# of included studies	# of included patients/ Patient characteristics	Setting(s)	Outcomes	Doses	Results	AMSTAR
Li et al, 2013[95]; Traditional Chinese Medicine/ Funding: Program for Innovative Research Team of Beijing University of Chinese Medicine (2011-CXTD-09) and the Project for Standard Operation Procedure of Clinical Appraisal in the Program for Significant New Drugs Development	Dec. 2012	12 RCTs	885 male and female adult patients (18 years and older) with a diagnosis of gout	Inpatient and/or Outpatient or NR	Pain relief	Traditional Chinese Medicine compared with colchicine (8 trials), allopurinol (4 trials), colchicine and allopurinol (3 trials), NSAID (12 trials), colchicine and NSAID (6 trials), allopurinol and NSAID (4 trials), uricosuric agents (1 trial), uricosuric and colchicines (1 trial), uricosuric and NSAID (2 trials).	There is not enough evidence showing that TCM was statistically more effective than conventional medications in pain relief [mean difference (MD), −0.03; 95 % confidence interval (CI), −0.06, 0.00],but TCM combined with conventional medicines may have better effectiveness (MD, −0.33; 95 %CI, −0.59, −0.07).	10/11
		2 RCTs	159 patients		Recurrence (calculated as the number of patients with at least one flare during the follow-up).		There was no evidence showing that TCM prevents gout recurrence better.	
		40 RCTs	2975 gout patients		Serum urate level reduction		The mean serum urate level after treatment in the intervention groups was 50.1 lower (54.37 to 45.83 lower) than the mean serum urate level after treatment in the control groups (MD −50.10 [−54.37, −45.83]).	
		10 RCTs	685 gout patients		Inflammation of joint swellings after treatment		The mean inflammation of joint swelling after treatment in the intervention groups was 0.14 lower (0.25 to 0.03 lower) compared with the mean inflammation of joint swelling after treatment in the control groups. MD −0.07 [−0.11,−0.02]	
		37 RCTs	NR		Adverse reactions		The current data show that TCM leads to fewer side reactions compared with conventional therapies [risk ratio (RR), 0.11; 95 % CI, 0.08 to 0.15].	

Author/Year/ Funding	Search End date	# of included studies	# of included patients/ Patient characteristics	Setting(s)	Outcomes	Doses	Results	AMSTAR
Zhou et al, 2013[96]; Traditional Chinese Medicine/ Funding: Natural Science Foundation of China	June 2012	17 RCTs	1042 patients diagnosed with primary gout in the phase of acute arthritis.	NR	clinical efficacy: Serum urate level reduction etc.	Chinese herbal decoctions (6-45g) vs traditional Western medicine[colchicine(0.5g/4-8g);Allopurinol (0.1 g*3); Ibuprofen (0.1 g*3);Diclofenac Sodium (25mg*3); Meloxicam (7.5mg); Indomethacin (25mg) etc]	The results of the meta-analysis showed that when gout had progressed to the stage of acute arthritis, there was no significant difference in clinical efficacy between Chinese herbal decoctions and traditional Western medicine, as indicated based on the following parameters: serum urate (standardized mean difference (SMD):0.35, 95% confidence interval (CI): 0.03 to 0.67), C reactive protein (SMD: 0.25, 95% CI: 20.18 to 0.69), erythrocyte sedimentation rate (SMD: 0.21, 95% CI: -0.02 to 0.45) and overall clinical response (relative risk (RR): 1.05, 95% CI: 1.01 to 1.10).	8/11
		7 RCTs	507 patients diagnosed with primary gout in the phase of acute arthritis		adverse reactions		The Chinese herbal decoction was significantly better than traditional Western medicine in controlling adverse drug reactions (RR: 0.06, 95% CI: 0.03 to 0.13).	
Lee et al, 2013[94]; Acupuncture/ Funding: National Research Foundation of Korea	August 2012	8 RCTs	632 patients with gouty arthritis	NR	Uric acid level reduction	Acupuncture [electro-acupuncture treatment (EAT) & acupuncture treatment (AT) 5-15days] in treatment group vs Western therapy [Allopurinol 350mg/day; Indomethacin 25mg; Probenecid 0.5 g/day; benzbromarone qd X6 days] in control group	The pooled analysis showed that acupuncture therapy alone decreased uric acid more than western therapy (MD = 30.37; 95% CI 4.28, 56.47; P<0.00001). Two out of the 8 trials (120 patients) reported a worse effect than the control group on uric acid.	9/11
		4 RCTs	380 patients with gouty arthritis		Visual Analogue Scale		The pooled analysis showed that acupuncture therapy alone improved the VAS more than western therapy (MD=2.23; 95% CI 1.39 - 3.08; P<0.0001).	
Khanna, et. al. 2014[47]; Traditional Chinese Medicine/Funding: ACR Gout Guidelines Grant	May 2013	30 RCTs (Only 2 relevant to Traditional Chinese Medicine)	Number of patients not reported; pooled mean age 54.14 (SD = 11.94); 89.7% male	NR	Joint swelling, Pain, serum urate	Danggui-Nian-Tong_Tang (DNTT) (6 tablets/day) vs Indomethacin (125mg/day) and Allopurinol (200mg/day); Simiao Pill vs Indomethacin (50mg per time, 3 times a day)	No significant improvement in reducing the number of painful and swollen joint (p<0.05) and pain score (p<0.01) by treatment with DGNTT compared with indomethacin. Also no significant reduction in serum urate level in DGNTT group (p>0.05) compared with allopurinol group (p<0.001); Simiao pill more efficacious than Indomethacin at Day 7 in reducing joint swelling and tenderness (p<0.05).	6/9

Author/Year/ Funding	Search End date	# of included studies	# of included patients/ Patient characteristics	Setting(s)	Outcomes	Doses	Results	AMSTAR
Choi et al., 2011[93]	May 2010	14 [2 on gouty arthritis]	NR		Gout specific response rate	NR	Ginger moxibustion plus leflunomide is more effective than leflunomide only. The response rates were significantly higher in the moxibustion plus drug group.	9/11

Evidence About Subgroups

No studies were identified that presented data stratified by gender, baseline or achieved serum urate, HLA-B5801 status, age, tophi, or comorbidities on the effectiveness of dietary advice for gout, specific dietary therapies, or TCM in management of gout.

Strength of Evidence

Gout-Specific Diets and Dietary Advice

We judged the strength of evidence for gout specific diets and dietary advice is insufficient to reach conclusions, as we identified only four small RCTs with three studies that had a high risk of bias.

TCM Including Herbs and Acupuncture

Although numerous RCTs of various herbal therapies or acupuncture were identified, the results of these studies are inconsistent, and the interventions all differ from study to study, making it impossible for us to draw any conclusions.

Key Question 3: Pharmacologic Management of Hyperuricemia in Gout Patients

a. In adults with gout, what are the benefits and harms of different pharmacological therapies on intermediate (serum and/or urine UA levels) and long-term clinical health outcomes (including recurrence of gout episodes and progression)?
b. Does effectiveness and comparative effectiveness of urate lowering therapy differ according to disease severity (including presence of tophi and baseline serum UA), underlying mechanisms of hyperuricemia, or baseline demographic and co-morbid characteristics?
c. What is the effect of dietary modification in combination with pharmacologic therapy?

Key Points

- High-strength evidence supports the finding that urate lowering therapy does not reduce the risk of acute gout attacks in the first 6 months.
- Moderate-strength evidence supports a reduction in the risk of acute gout attacks after about 1 year of urate lowering therapy.
- High-strength evidence supports the efficacy of urate lowering therapy in reducing serum urate.
- High-strength evidence supports the finding of no difference between 40mg febuxostat and 300mg allopurinol in serum urate lowering.

- Evidence is insufficient about the potential effect of the presence of tophi on the effectiveness and comparative effectiveness of allopurinol and febuxostat.
- High-strength evidence suggests that prophylactic therapy with low dose colchicine or low dose NSAIDs when beginning urate lowering therapy reduces the risk of acute gout attacks.
- Moderate-strength evidence supports the finding that longer courses of prophylaxis with colchicine or NSAIDs (> 8 weeks) are more effective than courses of shorter duration to prevent acute gout attacks when initiating urate lowering therapy.
- The SoE is insufficient that gout-specific dietary advice adds to the effectiveness of urate lowering therapy in reducing serum urate.
- The most common adverse event associated with allopurinol is a skin rash, occurring in up to 5 percent of patients. While most of these are mild and reversible, serious skin reactions including Topic Epidermal Necrolysis and Stevens Johnson Syndrome have been reported. Allopurinol has been proposed as a cause of the DRESS syndrome (Drug Rash with Eosinophilia and Systemic Symptoms. These serious side effects are sufficiently rare that clinical trials lack power to detect them. The risk of DRESS is greatly increased in patients with the HLA-B*5801 allele. Some evidence indicates that allopurinol reactions are more likely to occur in the first six months of treatment.
- Clinical expertise with febuxostat is less than with allopurinol. The most commonly reported adverse events in trials of febuxostat were abdominal pain, diarrhea, and musculoskeletal pain (5 percent-20 percent for each), but these rates were not statistically significantly different from those in placebo-treated patients. Rare skin reactions also occur with febuxostat.
- High-strength evidence supports a lack of difference in overall adverse events between allopurinol 300mg and febuxostat 40mg. A systematic review that identified four RCTs comparing the safety of urate lowering therapies found no statistically significant differences in overall adverse events between allopurinol and febuxostat.

Description of Included Studies

Placebo-controlled trials. Our literature search identified one SR[109] that included data from two placebo-controlled trials of allopurinol and two SRs[27, 110] that included data from two placebo-controlled trials of febuxostat. In addition, we identified one abstract of a febuxostat placebo-controlled trial[111], and one secondary analysis of a febuxostat placebo-controlled trial[112] already included in the systematic reviews. Finally, we identified one meta-analysis that compared the efficacy of febuxostat or allopurinol to that of placebo for female patients.[113]

Febuxostat versus Allopurinol. Our literature search identified six narrative SRs and one meta-analysis.[27, 109, 110, 113-116]. Four of the reviews were high quality (AMSTAR > 8),[27, 109, 110, 114] and two were low quality.[115, 117] The four high quality reviews included eight trials. The results of these studies were dominated by the FACT,[118] APEX,[119] CONFIRMS,[120] and EXCEL[121] trials. Our review identified one new randomized controlled trial that was not included in any of the prior systematic reviews.[122] We also identified a meta-analysis of the FACT, APEX, and CONFIRMS studies that assessed the comparative effectiveness of allopurinol and febuxostat in women with gout.[113]

Adverse events. We identified two SRs[123, 116] and 20 studies that reported on adverse events.[124-143]

Colchicine versus Allopurinol. Our literature search identified one new trial comparing colchicine with allopurinol.[63]

Allopurinol versus Probenecid. We identified one systematic review[144] that included one trial comparing probenecid with allopurinol.[145] We did not identify any new trials not covered in any of the existing systematic reviews.

Prophylaxis against acute gout attacks when starting urate lowering therapy. We identified two SRs [146, 147] and three original studies that addressed this issue.[55, 63, 148]

Dietary modification in addition to pharmacologic therapy. We identified one trial that addressed this kind of intervention.[106]

Detailed Synthesis

Placebo-Controlled Trials

Allopurinol Versus Placebo

Our literature search identified one SR[109] that included data from two placebo-controlled trials of allopurinol[58, 119] (see Table 11 for a description of the systematic reviews and Table 12 for descriptions of the two trials).

The first study, by Schumacher (2008),[119] was a 28-week double-blind RCT (the APEX trial) that compared allopurinol, febuxostat, and placebo. Participants were adults with hyperuricemia and gout with normal or impaired renal function. One hundred thirty-four patients were assigned to the placebo group and 268 patients were in the allopurinol 300mg group (patients with renal impairment received 100 mg allopurinol daily). The study found that the proportion of patients who achieved serum urate < 6.0mg/dl was significantly higher for than the allopurinol treated group than for the placebo group, and allopurinol resulted in greater reduction in serum urate level from baseline than did placebo. No significant difference was seen in gout attacks (flares), number of tophi, reduction in median tophus size, or incidence of adverse events between the two groups. Among the small sample of patients with renal impairment (who received allopurinol 100mg) and those in the placebo group, none achieved "last 3 monthly" serum urate levels < 6.0mg/dl, or attained serum urate < 6.0mg/dl at either the week-28 or final visits.

The second study, by Taylor et al. (2012),[58] was a 10-day double-blind RCT followed by an open label study from day 11 to day 30. Participants were adult males with crystal-proven gout who were experiencing an acute gout attack. Thirty-one patients were assigned to the allopurinol 300mg group and 26 were assigned to the placebo group. No differences in VAS pain scores or the incidence of recurrent gout attacks (flares) were found between the treatment and the placebo groups during the 10-day RCT period. Subgroup analysis comparing participants having a first gout attack with those having had prior attacks also revealed insignificant differences in pain scores. During the placebo-controlled period of the study, serum urate levels in the allopurinol group decreased significantly by day 10, whereas serum urate levels remained elevated in the

placebo group during this period. When open-label allopurinol was initiated in both groups on day 11, average serum urate decreased in both groups to similar levels: less than 6.0mg/dl by day 30.

Adverse Events Associated With Allopurinol

Allopurinol has a greater than 40 year history of use, and high level evidence of its harms in treatment of patients with gout and other conditions has been collected. The most common adverse event associated with allopurinol is a skin rash that occurs in up to 5 percent of patients. While most of these events are mild and reversible, serious skin reactions, including Topic Epidermal Necrolysis and Stevens Johnson Syndrome, have been reported. Allopurinol has been proposed as a cause of the DRESS syndrome (Drug Rash with Eosinophilia and Systemic Symptoms).[135, 137-139, 142] These serious side effects are sufficiently rare that clinical trials do not have sufficient power to detect them. In two placebo-controlled trials that included 268[119] and 26[58] patients treated with allopurinol, no statistically significant increases in skin reactions were observed in the allopurinol groups compared with the placebo group. Only one death was reported across both studies, that of an 80 year old male who had multiple medical problems.[58] In an analysis of VA databases, among approximately 200,000 patients treated with allopurinol, 150,000 patients treated with colchicine, and 3000 patients treated with febuxostat, using a multivariable Cox proportional hazards adjusting for demographics and comorbidities, the hazard ratio for DRESS was 1.86 (95% CI 1.55, 2.24), 2.17 (95% CI 0.90, 5.26), and 1.89 (95% CI 1.53, 2.33) respectively.[127] In another database analysis, this time of the French Pharmacovigilance Database (BNP), among nearly 1000 cases of toxic epidermal necrolysis or the Steven-Johnson Syndrome (90% of whom were adults), allopurinol use accounted for about 8% of cases.[125] The occurrence of DRESS associated with allopurinol is increased in patients with the HLA-B*5801 allele. An abstract from Taiwan, where the HLA-B*5801allele is more common than in the United States (21% of a sample of 2037), assessed prospectively the value of HLA typing in patients with gout or hyperuricemia. Among the 80 percent of patients who tested negative for the allele (N=1618), no cases of severe cutaneous adverse reactions were reported.[126] A retrospective case-control study of 70 cases of allopurinol hypersensitivity reactions found that 90 percent of cases occurred within 180 days of initiating allopurinol therapy and that cases had higher starting doses than controls (nearly 200 mg/day compared with approximately 100mg/day). The authors postulated that a "start low, go slow" prescribing practice would reduce the risk of serious adverse events.[143] The most commonly reported adverse events in these two trials were upper respiratory tract infections (19 percent) and musculoskeletal and connective tissue signs and symptoms (10 percent), but these rates were not statistically different from those of the placebo group (16 percent and 10 percent, respectively).[119] Therefore, our knowledge of serious AEs comes from case reports and case series.[123, 129-132] In one large series of patients (N=1,732) being treated with allopurinol for gout (93 percent male, 75 percent white, mean age=51 years, and mean BMI=34 kg/m^2), 3.0 percent of patients had serious treatment-emergent gout adverse events, death occurred in 0.2 percent; and 4.3 percent experienced adverse events leading to allopurinol withdrawal or study discontinuation.[140] HLA-B*5801 is associated with an increased risk of these serious side effects,[123, 128, 133, 141] and allopurinol requires a dose reduction in chronic kidney disease patients. A systematic review (AMSTAR rating 8 of 11) that compared the safety of ULT identified four RCTs that met inclusion criteria: No statistically significant differences were seen in overall adverse events between allopurinol and febuxostat.[116]

Febuxostat Versus Placebo

Our literature search identified two SRs[27, 110] that included data from two placebo-controlled trials of febuxostat (see Tables 10 and 11). In addition, we identified one new abstract of a febuxostat placebo-controlled trial[111] and one new secondary analysis of a febuxostat placebo-controlled trial already included in the systematic reviews (see Tables 13 and 14).

A total of two trials that evaluated the effect of febuxostat versus placebo for gout patients were included in the four SRs. The results of one trial are supplemented by a secondary subgroup analysis. The first study, by Becker et al. (2005b),[149] was a 28-day double-blind RCT with 38, 37, 40, and 38 patients assigned to placebo, febuxostat 40mg, febuxostat 80mg, and febuxostat 120mg, respectively (note that febuxostat doses above 80mg are not approved for use in the US). Adult patients with gout and hyperuricemia were enrolled. No difference in the overall incidence of gout attacks (flares) were observed between the 40mg febuxostat and placebo, but the incidence increased with dosage of febuxostat (43 percent with 80mg and 55 percent with 120mg). The incidence of gout attacks (flares) was lower (8-13 percent) for all groups when colchicine was administered with febuxostat or placebo. No difference in adverse events was found between febuxostat and placebo groups. All doses of febuxostat were associated with a significantly higher proportion of patients reaching target serum urate < 6.0mg/dl and a greater reduction in serum urate from baseline, with the 120mg febuxostat being the most effective. A five-year open label extension study of this trial found that the percentage of patients who required treatment for acute gout attacks decreased to less than 5 percent after about 12 months of ULT.134 As to treatment effect heterogeneity, significant pairwise differences in percentage reductions in serum urate between each of the febuxostat groups and the placebo group were observed regardless of baseline urinary uric acid production. Compared with either 80 or 120mg, patients with the highest baseline serum urate levels were less likely to reach a serum urate level < 6.0mg/dl when treated with 40mg/day of febuxostat on day 28. A secondary analysis by Goldfarb (2011)112 concluded that the percentage change in serum urate from baseline at day 28 was similar between overproducers and underexcretors among all febuxostat groups and was significantly greater than for the placebo group.

The second study, by Schumacher et al. (2008),119 was a 28-week double-blind RCT (the APEX trial) with 134 patients in the placebo group and 267, 269, and 134 patients in the febuxostat 80, 120 and 240mg groups, respectively (note again that febuxostat doses above 80mg are not approved for use in the US). Adults with hyperuricemia and gout, with normal or impaired renal function, were enrolled. Patients receiving higher doses of febuxostat were more likely to require treatment for gout attacks (flares) during the first 8 weeks when gout flare prophylaxis was provided, but no differences were observed in gout flares across treatment groups after prophylaxis ended, between weeks 8 and 28. There was no substantial difference in the number of tophi, the reduction in median tophus size, or adverse event rate across groups, with the exception that febuxostat 120mg achieved a higher mean percent decrease in the number of tophi compared with placebo at week 28. All doses of febuxostat were associated with a significantly higher proportion of patients reaching serum urate < 6.0mg/dl, with the 240mg febuxostat being the most effective.

Table 10. Randomized controlled trials included in systematic reviews (febuxostat vs. placebo)

RCTs	Systematic reviews	
	Tayar et al., 2012[27]	Ye et al., 2013[a110]
Becker et al., 2005[149] Goldfarb et al, 2011[112]	X	X
Schumacher et al., 2008[119]	X	X

[a]Two trials were excluded from our review that were included in Ye, et al., 2013 as the two trials excluded patient with gouty arthritis

Adverse Events Associated With Febuxostat

Clinical experience with febuxostat is much lower than with allopurinol. In the three placebo-controlled trials cited above, a total of 779 patients were treated with febuxostat, of which 210 received 120mg per day (higher than the FDA-approved maximum).[112, 119, 149] The most commonly reported adverse events in these trials were abdominal pain, diarrhea, and musculoskeletal pain (5 percent-20 percent for each), but the risks for these events were not statistically significantly different than for placebo-treated patients. No deaths were reported. Across all three studies, only one serious adverse event was judged by investigators to be related to febuxostat: an increase in serum creatinine from 1.1mg/dl to 1.5mg/dl while receiving 240mg/day, which decreased to 1.3mg/dl when the dose was reduced to 120mg/day.[119] In a one-year open label study of 171 Japanese men treated with febuxostat, four serious AEs were reported (gastric ulcer hemorrhage, spinal stenosis, sinusitis, and aggravated spinal osteoarthritis) but these were all judged to be unrelated to treatment. No deaths were reported.[136] Rare skin reactions also occur with febuxostat. One abstract reported that a prior reaction to febuxostat did not significantly increase the risk for a subsequent skin reaction; however, the 95% confidence was very wide, rendering any conclusion tentative, at best.[124]

According to the manufacturer, the following harms or cautions need to be considered with febuxostat:

- Febuxostat is contraindicated in patients being treated with azathioprine or mercaptopurine
- In the randomized controlled studies, patients treated with febuxostat had a higher rate of cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) (0.74 per 100 P-Y [0.36-1.37]) than those treated with allopurinol (0.60 per 100 P-Y [95% Cl 0.16-1.53]). A causal relationship with febuxostat has not been established. Providers are advised to monitor for signs and symptoms of myocardial infarction (MI) and stroke.
- Post-marketing reports have documented fatal and non-fatal hepatic failure in patients taking febuxostat, although the reports contain insufficient information necessary to establish the probable cause. Transaminase elevations greater than three times the upper limit of normal (ULN) were observed in RCTs (AST: 2%, 2%, and ALT: 3%, 2% in febuxostat and allopurinol-treated patients, respectively). No dose-effect relationship for these transaminase elevations was noted.
- The following adverse reactions occurred in 1 percent or more of febuxostat-treated patients and were at least 0.5 percent greater in frequency than in patients who received placebo in controlled studies: liver function abnormalities, nausea, arthralgia, and rash.

Evidence From New Studies

The only new study we identified that met inclusion criteria was published as an abstract only. This abstract reports results from a placebo-controlled trial of febuxostat. We did not identify any new studies that compared allopurinol with placebo.

Saag et al. (2013)111 conducted a RCT with 12-month follow up targeting gout patients with hyperuricemia and moderate-to-severe renal impairment. Thirty two patients each were randomly allocated to receive either febuxostat 30mg twice daily, febuxostat 40/80mg once daily, or placebo. Compared with placebo, febuxostat was associated with a higher proportion of patients achieving a serum urate < 6.0mg/dl and greater reduction in serum urate, with febuxostat 30mg twice daily being more effective than febuxostat 40/80mg once a day. The conclusions from the new RCT were consistent with SRs comparing febuxostat with placebo.

Evidence About Subgroups

We found only limited data about differences in effectiveness stratified by the prespecified subgroups:

- Chohan 2012[113] conducted a meta-analysis that compared the efficacy of febuxostat or allopurinol versus placebo for female patients, pooling data from three major RCTs (the FACT trial, APEX trial and CONFIRM trial). Female patients treated with either febuxostat or allopurinol were more likely to achieve serum urate < 6.0mg/dl than those treated with placebo. No female patients in the placebo group achieved target serum urate levels. The proportion of patients with AEs was similar across placebo, febuxostat, and allopurinol groups.
- Becker (2005) [149] stratified the sample by baseline serum urate levels and found that among patients with highest baseline serum urate, febuxostat 40mg was less effective in reducing serum urate levels than were 80 or 120mg.
- Schumacher (2008)[119] compared the effectiveness of febuxostat or allopurinol versus placebo in reducing serum urate in patients with mild to moderate renal impairment. The proportion of patients with impaired renal function who achieved target serum urate levels was numerically lower than among those with normal renal function across all treatment groups. The evidence is of low quality due to the very small sample of patients with impaired renal function (ranging from 5 to 11).

Table 11. Systematic reviews of febuxostat or allopurinol versus placebo for the management of chronic gout

Author/Year/ Funding	End Date of Search	# of Included Studies [indicate study design]	# of Included Patients/ Patient Characteristics Included	Setting(s)	Outcomes	Doses	Results	AMSTAR
Seth et al., 2014[109]; No external funding	January 2014	2 placebo-controlled trials of allopurinol	1072 (Schumacher 2008) + 57 (Taylor 2012); patients with chronic gout per ARA criteria	NR	Acute gout attacks, serum urate level, AEs	Allopurinol: 100/300mg Febuxostat: 80/120/240 mg	Compared with placebo, allopurinol (100 to 300mg daily) is not associated with a significant reduction in acute gout attacks, but increases the proportion of participants achieving sUA < 6.0mg/dl, without increasing withdrawals due to AEs or serious adverse event rates	11/11

Author/Year/ Funding	End Date of Search	# of Included Studies [indicate study design]	# of Included Patients/ Patient Characteristics Included	Setting(s)	Outcomes	Doses	Results	AMSTAR
Tayar et al., 2012[27]; No external funding	July 2011	4 placebo-controlled trials of febuxostat, 2 open-label extension trials of febuxostat	3978 chronic gout patients (Becker 2005a, 2005b, 2009, 2010; Schumacher 2008, 2009) - 2619 randomized to febuxostat, 172 to placebo and 1187 to allopurinol	NR	Frequency of gout flares, serum urate level, AEs	Febuxostat: 40/80/120/240mg	Compared with placebo, patients treated with all doses of febuxostat were more likely to achieve sUA < 6.0mg/dl; gout flares were more frequent among patients treated with febuxostat 120/240mg than those with placebo but there were no differences observed for 40/80mg; no statistically significant difference in AEs between any doses of febuxostat and placebo.	11/11
Ye et al., 2013[110]; National Natural Science Foundation of China	February 2012	4 placebo-controlled RCTs of febuxostat	1225 (Becker 2005, Schumacher 2008, Kamatani 2011-phase II, 2011-phase III); hyperuricemic (sUA >= 7mg/dl) adults with/without gout, mean age 47.5-52; 989 in febuxostat group and 236 in Placebo group	NR	Serum urate	Febuxostat: 20-240mg	All of the Febuxostat doses were associated with a significantly higher percent of patients achieving target serum urate levels.	10/11

Table 12. Randomized controlled trials of allopurinol versus placebo in the management of chronic gout

Author/Year	Population, Sample Size	Intervention	Outcomes	Timing	Results	Cochrane ROB
Schumacher et al., 2008[119]	Adults with hyperuricemia (serum urate level >8.0mg/dl) and gout (defined by the ACR criteria) with normal or impaired (serum creatinine level >1.5 to <2.0mg/dl) renal function. N = 1,072 (134 placebo, 268 allopurinol 300mg,) (For febuxostat vs. placebo results, see Table 13) 167 participating sites in the US; the majority of investigators were primary care physicians.	Allopurinol: 300mg Naproxen or colchicine was provided during the first 8 weeks	Proportion of participants with last 3 monthly serum urate levels < 6.0mg/dl; Proportion of subjects with serum urate level < 6.0mg/dl at week 28 or final visit; Percent reduction in serum urate level; Proportion of participants requiring treatment for gout flare; Total number and size of tophi; Adverse events	28 weeks	22% of individuals receiving allopurinol and 0% of those receiving placebo achieved last 3 monthly serum urate level < 6.0mg/dl (P < 0.001). 41% of those treated with allopurinol and 1% of those treated with placebo achieved serum urate level < 6.0mg/dl at the week 28 (P < 0.05). Allopurinol produced 34% reduction in serum urate level from baseline, compared with 4% reduction for those treated with placebo. During the first 8 weeks of the study, when gout flare prophylaxis was provided, 23% of those treated with allopurinol and 20% of those with placebo required treatment for gout flares. Between weeks 8 and 28, there were no statistically significant differences in the proportion of subjects requiring treatment for gout flares observed between the treatment groups. No significant difference between allopurinol and placebo in the number of tophi observed or the reduction in median tophus size. AEs occurred with similar frequency across treatment groups and were mild or moderate in severity.	1. Sequence: Low 2. Allocation concealment: High 3a. Blinding participants: Low 3b. Blinding care providers: Low 3c. Blinding outcome assessors: Low 4a. Follow-up less than 20%: High 4b. Loss to follow-up missing data explained: Low 4c. All participants randomized 5. Outcome reporting: Low 6. Findings reported as % who responded: Low

Author/Year	Population, Sample Size	Intervention	Outcomes	Timing	Results	Cochrane ROB
Taylor et al., 2012[58]	Adult male with crystal-proven gout based on ACR criteria and the presence of MSU crystals on arthrocentesis of the primary joint. N = 57 (31 allopurinol, 26 placebo) Veteran's Affairs Medical Center in White River Junction, Vermont.	Allopurinol: 300mg	Pain score measured by visual analogue scale for the primary affected joint on day 1 to 10; Self-reported gout flares in any joint during day 1 to 30; Adverse events	10 days (double blind, placebo-controlled); Day 11 - 30 (open label allopurinol 300mg)	Initial mean VAS pain scores for the allopurinol and placebo groups were 6.72 versus 6.28 (P = 0.37) decreasing to 0.18 versus 0.27 (P = 0.54) at day 10. Mean VAS pain scores did not statistically significantly differ between study groups at any point between days 1 and 10. Subgroup analysis comparing participants having a first gout attack versus those having had prior attacks revealed insignificant differences. No differences in the rate of new or recurrent gout flares between days 1 and 30 was observed - rates were 2 of 26 (7.7%) in the allopurinol group and 3 of 25 (12.0%) in the placebo group (P = 0.61). Elevation of serum creatinine > 1.5mg/dL occurred in 1 subject from each study arm. Colchicine reductions due to gastrointestinal symptoms occurred in 8 participants (31%) in the allopurinol group and 12 subjects (48%) in the placebo group. There was one death in the allopurinol group.	1. Sequence: Low 2. Allocation concealment: Low 3a. Blinding participants: Low 3b. Blinding care providers: Low 3c. Blinding outcome assessors: Low 4a. Follow-up less than 20%: Low 4b. Loss to follow-up missing data explained: Low 4c. Only those who completed the treatment program 5. Outcome reporting: Low 6. Findings reported as % who responded: Unclear

Table 13. Randomized controlled trials of febuxostat versus placebo in the management of chronic gout

Author/Year	Population, Sample Size	Intervention	Outcomes	Timing	Results	Cochrane ROB
Becker et al., 2005[149]	Adult patients with gout and hyperuricemia (sUA > 8.0mg/dl). All patients met the ACR criteria for the classification of the acute arthritis of primary gout. N = 153 (38 placebo, 37 febuxostat 40mg, 40 febuxostat 80mg, 38 febuxostat 120mg) Setting unclear.	Febuxostat: 40/80/120mg Colchicine prophylaxis, 0.6mg twice daily, was provided during the 2-week washout period and the first 2 weeks of double-blind treatment	Proportion of participants with serum urate levels < 6.0mg/dl; Percent reduction in serum urate level; Incidence of gout flares	28 days	56%, 76% and 94% of individuals treated with febuxostat 40, 80 and 120mg, respectively, achieved serum urate acid < 6.0mg/dl on day 28, compared with none in the placebo group ($p < 0.001$). Compared with either 80 or 120mg, patients with the highest baseline sUA levels were less likely to reach a sUA level < 6.0mg/dl when treated with 40mg/day of febuxostat on day 28. The mean percentage reductions in sUA from baseline levels were significantly greater in each febuxostat group than in the placebo group, regardless of baseline urinary uric acid production. The greatest reductions in the febuxostat group receiving 120mg/day (range of mean change 53–59% at each visit). The overall incidence of gout flares were similar in the placebo group (37%) and 40mg febuxostat group (35%) but higher in the 80mg febuxostat (43%) and the 120mg febuxostat group (55%). The incidence of gout flares was lower (i.e., 8-13%) when treatment was administered with colchicine and higher when administered alone. When administered alone, higher doses of febuxostat were associated with higher incidence of gout flares (34%, 30%, 40%, 42% for placebo, febuxostat 40, 80 and 120mg, respectively).	1. Sequence: Low 2. Allocation concealment: High 3a. Blinding participants: Low 3b. Blinding care providers: Unclear 3c. Blinding outcome assessors: Low 4a. Follow-up less than 20%: Low 4b. Loss to follow-up missing data explained: Low 4c. All participants randomized to particular groups 5. Outcome reporting: Low 6. Findings reported as % who responded: Low

Author/Year	Population, Sample Size	Intervention	Outcomes	Timing	Results	Cochrane ROB
					No significant differences between the febuxostat and placebo groups in the overall incidence of treatment-related adverse events, with the majority of events being mild or moderate in severity.	
Goldfarb et al., 2011[112] Subgroup analysis of Becker, 2005b.	Adult patients with gout and hyperuricemia (sUA 8.0mg/dl). All patients met the ACR preliminary criteria for the classification of the acute arthritis of primary gout. N = 153 (38 placebo, 37 febuxostat 40mg, 40 febuxostat 80mg, 38 febuxostat 120mg) Setting unclear.	Febuxostat: 40/80/120mg Colchicine prophylaxis, 0.6mg twice daily, was provided during the washout period and the first 2 weeks of double-blind treatment	Proportion of subjects with serum urate levels < 6.0mg/dl at day 28; Percentage change in serum urate from baseline to day 28	28 days	Treatment with any dose of febuxostat led to the majority of participants achieving sUA < 6.0mg/dl on day 28 in both overproducers and underexcretors; febuxostat 40mg appeared to be more efficacious in overproducers (sample size too small to perform statistical test). The percentage change in serum urate from baseline to day 28 was similar between overproducers and underexcretors among all treatment groups.	1. Sequence: Low 2. Allocation concealment: High 3a. Blinding participants: Low 3b. Blinding care providers: Low 3c. Blinding outcome assessors: Low 4a. Follow-up less than 20%: Low 4b. Loss to follow-up missing data explained: Low 4c. Only those who had baseline sUA 5. Outcome reporting: Low 6. Findings reported as % who responded: Low
Schumacher et al., 2008[119]	Adults with hyperuricemia (serum urate level >8.0mg/dl) and gout (defined by the ACR criteria) with normal or impaired (serum creatinine level >1.5 to <2.0mg/dl) renal function. N = 1,072 (134	Febuxostat: 80/120/240mg Placebo Naproxen or colchicine was provided during the first 8 weeks.	Proportion of participants with last 3 monthly serum urate levels < 6.0mg/dl; Proportion of participants with serum	28 weeks	48%, 65% and 69% of individuals treated with febuxostat 80, 120 and 240mg, respectively, achieved last 3 monthly serum urate levels < 6.0mg/dl; none of those with placebo did ($p < 0.001$). The proportions of participants with impaired renal function attaining last 3 monthly serum urate levels < 6.0mg/dl were 44% (4 out of 9 patients with impaired renal function) in the febuxostat 80mg group, 46% (5 out of 11) in the	1. Sequence: Low 2. Allocation concealment: High 3a. Blinding participants: Low 3b. Blinding care providers: Unclear 3c. Blinding outcome assessors: Low 4a. Follow-up less than 20%: High 4b. Loss to follow-up missing data

Author/Year	Population, Sample Size	Intervention	Outcomes	Timing	Results	Cochrane ROB
	placebo, 267 febuxostat 80mg, 269 febuxostat 120mg, 134 febuxostat 240mg) (For allopurinol vs. placebo results, see Table 12) 167 participating sites in the US; the majority of investigators were primary care physicians.		urate level < 6.0mg/dl at week 28 or final visit; Percent reduction in serum urate level; Proportion of participants requiring treatment for gout flare; Total number and size of tophi; Adverse events		120mg group, and 60% (3 out of 5) in the 240mg group. At week 28, 76%, 87% and 94% of participants treated with febuxostat 80, 120 and 240mg, respectively, achieved serum urate levels < 6.0mg/dl, whereas 1% of those treated with placebo achieved the same goal ($p < 0.05$). No statistically significant differences in the proportion of participants requiring treatment for gout flares observed between treatment groups between weeks 8 and 28. During the first 8 weeks, when gout flare prophylaxis was provided, greater proportions ($p < 0.05$) of participants receiving febuxostat 120mg (36%) and 240mg (46%) required treatment for gout flares, compared with those receiving febuxostat 80mg (28%) or placebo (20%). No significant difference between febuxostat and placebo in the number of tophi observed or the reduction in median tophus size, except for a significant mean percent decrease in the number of tophi observed with febuxostat 120mg (-1.2) versus placebo (-0.3) at week 28 ($P < 0.05$). AEs occurred with similar frequency across treatment groups and were mild or moderate in severity.	explained: Low 4c. All participants randomized 5. Outcome reporting: Low 6. Findings reported as % who responded: Low

Table 14. Randomized controlled trials of febuxostat versus placebo for the management of chronic gout not included in existing systematic reviews

Author/Year	Population, Sample Size	Intervention	Outcomes	Timing	Results	Cochrane ROB
Saag et al., 2013[111] Abstract only	Gout patients with hyperuricemia and moderate-to-severe renal impairment fulfilling ARA criteria, patients with tophi were excluded N = 96 (32 placebo, 32 febuxostat 30mg BID, 32 febuxostat 40/80mg QD) Setting unclear.	Febuxostat: 30mg BID Febuxostat: 40/80mg QD (titrated from FEB 40mg to 80mg QD based on day 14 sUA)	Proportion of subjects with serum urate <6.0mg/dL; Change from baseline in serum urate and estimated glomerular filtration rate (eGFR); Adverse events	12 months	The proportion of participants with sUA < 6.0mg/dL at month 12 was 69%, 45%, and 0% for febuxostat 30mg BID, febuxostat 40/80mg QD, and PLB, respectively (P < 0.001 vs. placebo). Change in serum urate from baseline was -5.1, -4.3 and 0.07 at month 6, and -5.0, -4.2 and -0.15 at month 12 for febuxostat 30mg BID, febuxostat 40/80mg QD, and PLB, respectively (P < 0.001 vs placebo). Mean eGFR change from baseline at month 12 was not significant different across groups. The majority of AEs were mild to moderate in intensity and not considered to be related to study treatment.	1. Sequence: Low 2. Allocation concealment: High 3a. Blinding participants: Low 3b. Blinding care providers: Low 3c. Blinding outcome assessors: Low 4a. Follow-up less than 20%: Unclear 4b. Loss to follow-up missing data explained: Unclear 4c. Unclear if all participants were randomized 5. Outcome reporting: Low 6. Findings reported as % who responded: Low

Comparative Effectiveness

Febuxostat Versus Allopurinol

Systematic Reviews Comparing the Effectiveness of Febuxostat and Allopurinol

Four high quality SRs (AMSTAR > 8) reviewed the comparative efficacy of febuxostat and allopurinol.[27, 109, 110, 114] The results of these reviews were broadly consistent, and the results of these studies were dominated by the FACT,[118] APEX,[119] CONFIRMS,[120] and EXCEL[121] trials (see Tables 15 and 16).

In terms of clinical outcomes, gout flare incidence was higher at high doses of febuxostat (120mg or 240mg) than with allopurinol 100-300mg. Gout flare incidence was not statistically different between febuxostat 40mg, febuxostat 80mg, and allopurinol (100-300mg). Observed changes in tophi were less consistent. One review concluded that tophus area reduction was greater in patients taking febuxostat than in those taking allopurinol, but the median reduction in the number of tophi did not differ between these groups.[27] Other reviews reported non-significant differences in tophi changes and resolution.[109, 114]

Conclusions about adverse events also varied. One review found that the high-dose febuxostat (240mg) groups experienced more adverse events than patients taking allopurinol, but the allopurinol groups had more adverse events when compared with febuxostat 80mg (note that febuxostat doses above 80mg are not approved for use in the US). When all doses were analyzed together, adverse event rates did not differ between febuxostat and allopurinol.

The research biomarker outcome results for serum urate level were consistent across these reviews: Patients taking febuxostat at doses of 80mg or higher were more likely than patients taking allopurinol 100-300mg to reach target serum urate levels of less than 6.0mg/dl.

One SR[110] assessed the comparative effectiveness and safety of febuxostat and allopurinol in patients with and without gout. Patients taking febuxostat were more likely than patients taking allopurinol to achieve target sUA level <=6.0mg/dL at the final visit (all doses analyzed together). The proportion achieving target serum urate increased with the febuxostat dose (40mg: OR 1.2, 95% CI [1.05, 1.49], 80mg: OR 3.27, 95% CI [2.14-5.00], 120mg: OR 6.67 95% CI [5.23, 8.51]. There were no significant differences in AEs between the two groups: Pooled data demonstrate that both febuxostat and allopurinol groups had similar rates of AEs, which were mostly mild or moderate in severity. In the febuxostat groups, the most common AE that led to study withdrawal was elevated liver enzymes and the most frequent serious AEs were cardiovascular in nature.

One low-quality SR was also identified whose results were broadly consistent with those of the high-quality SRs.[115]

We also identified an SR that specifically compared the safety of urate lowering drugs. This 2014 review included seven RCTs and four SRs. Two of the included studies compared allopurinol with benzbromarone, a drug not included in our scope. The other five RCTs are all described below.[118-120, 136, 150] This review concluded that total AEs did not differ significantly between allopurinol and febuxostat (pooled relative risk =1.04, 95% CI, 0.98, 1.11) (AMSTAR of 8/11).[116]

We also identified a SR of gout treatments in patients with impaired renal function (AMSTAR of 7/9).[117]

Table 15. Randomized controlled trials included in systematic reviews

RCTs	Systematic reviews					
	Tayar et al., 2012[27]	Faruque et al., 2013[114]	Ye, et al., [110] Hyperuricemia with and without gout	Seth et al., 2014[109]	Manara et al., 2013[115]	Van Echteld et al., 2014[117]
Singal et al., 2011[151] Bangladesh				X	X	
Becker et al., 2010[120] CONFIRMS	X	X	X	X	X	X
Kamatani et al., 2011[150] Japan		X	X		X	
Schumacher et al., 2008[119] APEX	X	X	X	X	X	X
Becker et al., 2009[121] EXCEL	X		X			
Becker et al., 2005[118] FACT	X	X	X	X	X	
Whelton et al., 2010[152] Renal impairment	X					
Naoyuki et al., 2011[153]		X	X			

Major RCTs Comparing Effectiveness of Febuxostat and Allopurinol

All SRs we identified that compared the efficacy of febuxostat with allopurinol included data from the FACT[118] and APEX[119] clinical trials, with later SRs also including CONFIRMS[120] and EXCEL.[121] The results of the SRs are dominated by these studies, because of the small sample sizes of other included trials. Trials included in at least one SR were Singal (2011)[151], Kamatani (2011)[150], and Naoyuki (2011).[153] We also included one abstract.[152] The most important trials, FACT, APEX, CONFIRMS, and EXCEL, are summarized here. All of these trials used gout flare prophylaxis during the study period. FACT, APEX, and EXCEL withdrew prophylaxis after week eight. CONFIRMS prescribed prophylaxis for the entire study duration.

The FACT trial[118] compared 760 patients who received either febuxostat (80 or 120mg) or allopurinol (300mg) daily for 52 weeks (note that febuxostat doses above 80mg are not approved for use in the US). No statistically significant differences in clinical outcomes were found. The overall incidence of gout attacks (flares) was similar in all groups (64 percent, 70 percent, and 64 percent, respectively) from weeks 9 to 52 (p=0.23 for febuxostat 120mg vs. allopurinol). The median reductions in tophus area were 83 percent, 66 percent, and 50 percent, respectively (p=0.08 for febuxostat 80mg vs. allopurinol, p=0.16 for febuxostat 120mg vs. allopurinol). More patients in the febuxostat 120mg group than in the allopurinol group (p=0.003) or the febuxostat 80mg group discontinued the study. Four of the 507 patients in the febuxostat groups (0.8 percent) died, compared with none in the allopurinol group (p=0.31). The outcome of achieving a target serum urate level of <6.0mg/dl was greater for the febuxostat groups than for the allopurinol group (53 percent, 62 percent, and 21 percent, respectively; p<0.001 for comparing each febuxostat group to allopurinol).

The APEX trial[119] compared 1,072 patients over 28 weeks who received either febuxostat (80, 120, or 240mg/day), allopurinol (100mg or 300mg per day, based on renal function), or placebo. No differences were observed between the groups in the proportion of participants with gout attacks (flares) who required treatment between weeks 8 and 28. During the first 8 weeks of the study (when gout flare prophylaxis was provided), more patients in the high-dose (120 and 240mg) febuxostat groups required treatment for gout attacks (flares) (36 percent and 46 percent) compared with those in the febuxostat 80mg (28 percent) and allopurinol (23 percent) groups ($p<0.05$). No significant differences in number of tophi were observed between the allopurinol and febuxostat groups. Reductions in median tophus size were reported in all treatment groups, but no significant differences were seen between the allopurinol, febuxostat, or placebo groups. The only difference in the decrease in number of tophi was between the febuxostat 120mg group (-1.2) and the placebo group (-0.3) at the end of the study ($p<0.05$). Proportions of adverse events were similar across groups, except for dizziness and diarrhea, which were more frequent in the febuxostat 240mg group. The outcome of achieving serum urate levels <6.0mg/dl for the last three months of the study was observed in 48 percent of the febuxostat 80mg group, 65 percent of the febuxostat 120mg group, and 69 percent of the febuxostat 240mg group, which was significantly higher than the number who achieved that outcome in the allopurinol group (22 percent). In patients with impaired renal function, more patients treated with febuxostat (all doses) achieved a serum urate of <6.0mg/dl than patients taking allopurinol 100mg.

The CONFIRMS trial[120] compared 2,268 patients receiving febuxostat 40mg per day, febuxostat 80mg per day, and allopurinol 200 or 300mg per day (depending on renal function). The only clinical outcomes reported were gout flare and safety outcomes. Rates of flare requiring treatment occurred in 10 percent to 15 percent of patients in all groups during the first two months and declined during the trial. No statistically significant differences were seen between groups. Prior use of ULT was associated with lower rates of flare compared with those without prior use ($p<0.001$), for each comparison. Adverse events were reported by 56 percent of participants, but the rates of occurrence did not differ among the treatment groups, and most events were mild or moderate. The outcome of serum urate level <6.0mg/dl at six months was reached in 45 percent of the febuxostat 40mg group, 67 percent of the febuxostat 80mg group, and 42 percent of the allopurinol group ($p<0.001$ for febuxostat 80mg compared with both of the other groups). Febuxostat 80mg was similarly superior in patients with mild to moderate renal impairment, although febuxostat 40mg was superior to allopurinol in these patients as well.

The EXCEL trial[121] is an open-label extension study of two phase III trials, in which 1,086 patients received febuxostat 80 or 120mg or allopurinol 300mg for up to 40 months. Gout attacks (flares) increased after prophylaxis withdrawal in week 8, but flare rates decreased over time in all treatment groups. Gout flare was reported in less than 4 percent of participants after 18 months of treatment. Participants with tophi who maintained the target serum urate level over time experienced greater reductions in the areas of index tophi, the number of tophi, and index tophi resolution. Baseline tophus resolution was achieved by 46 percent, 36 percent, and 29 percent of participants maintained on febuxostat 80mg, febuxostat 120mg, and allopurinol, respectively. Overall adverse event rates were similar among the treatment groups. After one month of initial treatment, 81 percent and 87 percent of patients receiving 80mg and 120mg febuxostat achieved serum urate < 6.0mg/dl, as compared with 46 percent for patients receiving allopurinol. To achieve a serum urate <6.0mg/dl, more participants originally assigned to allopurinol switched to febuxostat than the number who switched from febuxostat to allopurinol.

RCTs not Included in any Systematic Review

We identified one new RCT[122] that compared febuxostat and allopurinol in patients with chronic gout (see Table 17). This study randomized 512 Chinese gout patients to febuxostat 40mg, febuxostat 80mg, or allopurinol 300mg for 28 weeks, with flare prophylaxis provided through week 8. No significant changes in the number of tophi were observed at the final visit from baseline in all treatment groups. The rates of gout flares requiring treatment from weeks 9 through 28 and incidence of adverse events were similar among all groups. The endpoint of serum urate <6.0mg/dl for the last 3 months was reached in 45 percent of patients receiving 80mg of febuxostat, 27 percent of those receiving febuxostat 40mg, and 24 percent of those receiving allopurinol. Efficacy of febuxostat 80mg at reducing serum urate was higher than that of the other groups ($p<0.001$); allopurinol and febuxostat 40mg were equally effective.

Evidence About Subgroups

No studies stratified results by HLA-B5801 status. One study stratified results by presence of tophi at baseline.[120] Two studies[118, 120] stratified results by baseline serum urate. Two studies[119, 120] stratified results by renal function. Four studies[154-157] were identified that compared the effectiveness of febuxostat and allopurinol in various subpopulations of the CONFIRMS trial, including diabetics, older versus younger patients, the elderly, and African Americans. One study performed a meta-analysis of the FACT, APEX, and CONFIRMS studies to assess the comparative efficacy of allopurinol and febuxostat in women with gout.[113]

Presence of Tophi at Baseline

Becker (2010)[120] stratified results for achievement of target serum urate by presence of tophi at baseline. Overall, the presence of tophi was associated with lower rates of achieving target serum urate level. Among patients with baseline tophi,, those taking febuxostat 80mg were more likely to achieve target serum urate (57 percent) than patients taking febuxostat 40mg or allopurinol 200-300mg (35 percent and 32 percent). In comparison, patients without tophi at baseline achieved target serum urate levels at rates of 70 percent, 48 percent, and 45 percent, respectively.

Baseline Serum Urate

Becker (2005)[118] stratified results for achievement of target serum urate by serum urate level at baseline. At all levels of baseline serum urate levels, febuxostat 80mg was more effective than allopurinol 300mg for achieving target serum urate (47 percent for those with baseline serum urate ≥10.0mg/dl and 57 percent for those with baseline serum urate <9.0mg/dl for febuxostat versus 8 percent for those with serum urate ≥10.0mg/dl and 40 percent for those with serum urate <9.0mg/dl for allopurinol). Becker (2010)[120] also stratified results for achievement of target serum urate by serum urate level at baseline. Patients with high baseline serum urate achieved target serum urate levels at lower rates than those with lower baseline serum urate. Febuxostat 80mg was more effective for reaching target serum urate among people with high baseline serum urate (>9.0mg/dl) (49 percent to70 percent) compared with febuxostat 40mg (26 percent to 47 percent) or allopurinol 200-300mg (31 percent to 40 percent).

Renal Function

Becker (2010)[120] stratified results for achievement of target serum urate by renal function at baseline. Compared with patients with normal renal function, patients with mild renal impairment

taking either febuxostat or allopurinol were more likely to achieve target serum urate. Across treatment groups, about 71 percent of patients with mild or moderate renal impairment achieved target serum urate levels while taking febuxostat 80mg, compared with 43-52 percent of patients taking febuxostat 40mg or 31-46 percent of patients taking allopurinol 200-300mg. Schumacher (2008)[119] observed similar comparative efficacy with febuxostat 80mg compared with allopurinol, but this finding was based on a small number of observations. A SR of gout treatments in patients with impaired renal function also identified only these two trials of allopurinol versus febuxostat compared with placebo (AMSTAR rating of 7 of 9).[117]

Gibson (1981)[158] randomized 59 patients to receive either 0.5mg colchicine (twice daily) or allopurinol (200mg) and colchicine. Patients were followed for up to two years. The mean glomerular filtration rate (GFR) was statistically significantly lower in the colchicine group and declined over the study period as compared with the allopurinol group in which GFR increased slightly. Urate clearance fell in both groups but the trend was significant only in the group that received colchicine plus allopurinol. The study monitored renal function, including blood urea concentration, serum creatinine, GFR, urine concentrating ability, number of patients with proteinuria, and severity of proteinuria. For a subgroup of patients receiving colchicine who had achieved reductions in GFR of more than 10ml/min/(1x73 m^2), the results were stratified by age and presence or absence of hypertension.

Age

Becker (2011)[154] performed a secondary analysis of the CONFIRMS trial to compare efficacy of febuxostat and allopurinol in the elderly (>65 years) with that of younger patients (<65 years). Among 374 older subjects, the efficacy of both drugs was comparable in younger and older patients and both drugs were well tolerated in spite of high comorbidity rates and renal impairment in this group. Among patients with mild renal impairment and within each treatment group, urate lowering efficacy was higher in patients aged 65 and older than in younger patients. Among patients with moderate renal impairment, older patients within the 40 and 80mg febuxostat groups were more likely to achieve target serum urate than younger patients, but this age difference was not observed for allopurinol treatment.

Jackson (2012),[156] another secondary analysis of the CONFIRMS data, assessed treatment efficacy in the elderly subgroup only. Febuxostat 80mg was significantly more efficacious (82 percent) than febuxostat 40mg (62 percent; $p < 0.001$) or allopurinol (47 percent; $p < 0.001$) for achieving the primary efficacy endpoint of serum urate <6.0mg/dl. Rates of AEs were low and comparable across treatments.

Race

Wells (2012)[157] was a secondary analysis of 228 African Americans in the CONFIRMS trial. African American patients were mostly male and obese and were more likely to have diabetes, renal impairment, and cardiovascular disease. Rates of adverse events, gout flare, and efficacy in all treatment groups, were comparable between African American and Caucasian patients, regardless of renal function. Febuxostat 80mg was more effective than febuxostat 40mg or allopurinol 200/300mg in African American patients with mild or moderate renal impairment.

Gender

Chohan (2012)[113] was a retrospective analysis of the FACT, APEX, and CONFIRMS trials that compared the efficacy of allopurinol and febuxostat in 226 women with gout. Women

enrolled in these studies were older, and were more likely to be obese and to have renal impairment, hypertension, hyperlipidemia, and diabetes than the population average. Tophus resolution and incidence of gout flare were not reported. The proportions of women achieving serum urate levels <6.0mg/dl were greater in all febuxostat dosage groups compared with the allopurinol group, with efficacy significantly greater in the 80mg ($p<0.001$) and 120mg ($p=0.006$) groups. Efficacy results were similar among women with mild renal impairment, but low-dose febuxostat (40mg) was even less efficacious than higher dose febuxostat in female patients with moderate/severe renal impairment. However the number of patients in most of the renal function subgroups was small and the evidence should be interpreted with caution. Adverse event rates were similar across groups. The most common adverse events were upper respiratory tract infections, musculoskeletal/connective tissue disorders, and diarrhea.

Diabetes

Becker (2013)[155] performed a secondary analysis of the CONFIRMS trial that compared the efficacy of gout drugs in 312 diabetic and 1957 non-diabetic patients. Diabetic gout patients were older, more likely to be female, and had longer gout duration than non-diabetic patients. Comorbidities were more common among diabetics, including cardiovascular disease, impaired renal function, hyperlipidemia, and obesity. The efficacy of febuxostat 80mg exceeded that of febuxostat 40mg or allopurinol ($p <0.050$) at all levels of renal function, achieving target serum urate levels in most diabetic and non-diabetic patients. Similar adverse events were reported by both diabetic and non-diabetic patients.

Table 16. Systematic reviews of febuxostat versus allopurinol for the management of chronic gout

Author/ Year Funding	End Date of Search	# of Included Studies	# of Included Patients/ Participant Characteristics	Setting	Doses	Outcomes	Results	AMSTAR
Manara, 2013[115] No external funding	March 2012	NR	NR	NR	FEB: 40, 80, 120, 240mg/day, ALL:100, 200, 300mg/day	Achievement of sUA <6.0, gout attacks, AEs	Febuxostat is an effective urate lowering agent in patients with gout and has shown greater efficacy at a dosage of 80mg or more when compared with allopurinol at the maximum dose of 300mg in the short-term control of hyperuricaemia. Treatment with febuxostat has been shown to be safer in patients with mild or moderate renal insufficiency when compared with treatment with allopurinol.	2/11
Tayar, 2012[27] No external funding	July 2011	4	3,978 patients at least 16 years old meeting ACR for acute arthritis of primary gout, or diagnosis as described by the authors	Multiple primary care centers, United States and Canada	FEB: 40, 60, 80, 120, 240mg/day ALL: 100, 200, 300mg/day	Gout flare, proportion of patients with sUA <6.0mg/dl AEs, tophus burden,	FEB 40mg vs ALL: groups did not differ by gout flare incidence, achievement of sUA <6mg/dl, or AEs. FEB 80mg vs ALL: groups did not differ by gout flare incidence, but febuxostat patients more likely to achieve sUA <6mg/dl, but reduction of sUA from baseline was not statistically significant. Allopurinol group had more AEs. FEB 120/240mg vs ALL: febuxostat group had more gout flares, but also more likely to achieve sUA <6mg/dl, and there was a statistically significant reduction of sUA from baseline. AEs higher in allopurinol compared with febuxostat 120mg, but AEs were higher than allopurinol at 240mg. All doses: Tophus area reduction was greater in the febuxostat groups, but the proportion of patients with a reduction and the median reduction on the number of tophi were similar. There was no statistically significant difference in harms at 3 years.	11/11

Author/ Year Funding	End Date of Search	# of Included Studies	# of Included Patients/ Participant Characteristics	Setting	Doses	Outcomes	Results	AMSTAR
Faruque, 2013[114] Alberta Heritage Foundation for Medical Research and University Hospital Foundation	Feb 2012	5	4,250 patients of all ages with chronic gout (MSU crystals or 6/12 ACR)	Multiple	FEB: 40, 60, 80, 120, 240mg/day ALL: 100, 200, 300mg/day	Proportion of gout glares, proportion achieving target serum urate (<6mg/dl), patient and physician global assessment, tophus resolution, AEs	Patients were more likely to have a gout flare on febuxostat compared with allopurinol, but this difference depends on the dose (high-dose febuxostat produced a high risk of flare while low dose <=80mg/day was similar to allopurinol in flare frequency). Febuxostat recipients had a lower risk of adverse events compared with those on allopurinol. Patients on febuxostat were more likely to reach target serum urate levels. Tophus changes were not significantly different.	10/11
Ye, 2013[110] National Natural Science Foundation of China	Feb 2012	7 RCTs (10 total studies, 7 for ALL vs. FEB	5,690 Adults >=18 years with hyperuricemia (SUA >=7mg/dl) with and without gout	NR	ALL: 100-300mg/day FEB: 40-240mg/day	Achievement of target serum urate (<6mg/dl), AEs	SUA target reached in more people in febuxostat group. No difference in AE outcomes Compared with the allopurinol group, the proportion of patients who achieved a target sUA level <=6.0mg/dL at the final visit was higher in the febuxostat-treated group. There were no significant differences in AEs between the two groups.	10/11
Seth, 2014[109] No external funding	Jan 2014	4 comparing allopurinol with febuxostat	4203 adults with chronic gout	NR	FEB: 40, 80, 120, 240mg/day, ALL:100, 200, 300mg/day	AEs, SAEs, gout attacks, achievement of target sUA <6mg/dl, tophus resolution	Similar rates of AEs, SEAs, and gout attacks were found when allopurinol was compared with febuxostat (80mg/day). Gout attacks were higher in febuxostat at higher doses (>80 md/day) than allopurinol. Allopurinol was less successful than febuxostat at achieving sUA < 6mg/dl. Tophus resolution was also similar for allopurinol (200-300mg/day) and febuxostat (80 md/day).	10/10

Author/ Year Funding	End Date of Search	# of Included Studies	# of Included Patients/ Participant Characteristics	Setting	Doses	Outcomes	Results	AMSTAR
van Echteld, 2014[117]	October 2011	2 comparing allopurinol with febuxostat	18 years of age with gout and at least 1 of the defined comorbidities or comedications (renal disease, hematologic malignancy, ischemic heart disease, cardiac failure, hypertension, dyspepsia, ulcer-related disorders, metabolic syndrome, and diabetes mellitus)	NR	FEB: 40, 80 ALL: 100, 300	SUA	No differences in adverse events between the patient group with normal and those with impaired renal function. There were also no differences between the patient groups receiving febuxostat in different doses and allopurinol in different doses.	7/9

Table 17. Randomized controlled trials of febuxostat versus allopurinol or colchicine versus allopurinol for the management of chronic gout not included in existing systematic reviews

Author/Year	Population, Sample Size	Intervention	Outcomes	Timing	Results	Cochrane ROB
Huang 2014[122] Febuxostat vs. allopurinol	516 patients (18-70 years) with gout (ACR criteria) and sUA >8.0mg/dl Chronic 14 sites in China (care setting NR)	Febuxostat 40mg/day Febuxostat 80mg/day Allopurinol 300mg/day	sUA <6.0mg/dl at 20, 24, and 28 weeks Reduction of sUA from baseline Tophi resolution Gout flares requiring treatment AEs	2, 6, 10, 14, 16, 20, 24, and 28 weeks	27.33%, 44.77%, and 23.84% of patients in the febuxostat 40mg, 80mg, and allopurinol groups reached target sUA, respectively. Febuxostat 80mg also achieved higher reductions in sUA from baseline. Groups did not differ on tophus resolution, gout flare, or AEs.	1. Sequence: Low 2. Allocation concealment: Low 3a. Blinding participants: Low 3b. Blinding care providers: Low 3c. Blinding outcome assessors: Low 4a. Follow-up less than 20%: Low 4b. Loss to follow-up missing data explained: Low 4c. All participants randomized 5. Outcome reporting: Unclear 6. Findings reported as % who responded: Yes
Gibson 1982[158] Colchicine vs. allopurinol	N=59, with at least one acute gouty arthritis attack.	Colchicine (0.5mg/day x 2) vs. Colchicine + Allopurinol (200mg/day)	glomerular filtration rate, blood urea, blood creatinine, renal calculi, urine concentrating ability, urine pH, plasma uric acid	1 year, 2 year	Greater decline of mean GFR in colchicine group; Greater decline of plasma uric acid in allopurinol group; Greater decline and sharper trend decline for urate clearance in allopurinol group	1. Sequence: Low 2. Allocation concealment: High 3a. Blinding participants: High 3b. Blinding care providers: High 3c. Blinding outcome assessors: High 4a. Follow-up less than 20%: Low 4b. Loss to follow-up missing data explained: Low 4c. Only those who completed the treatment program 5. Outcome reporting: Low 6. Findings reported as % who responded: Unclear

Allopurinol Versus Probenecid

We identified one SR that examined the comparative efficacy of probenecid and allopurinol.[144] Only one study[145] that compared probenecid and allopurinol was included in that review. In terms of clinical outcomes, the effects of allopurinol on the frequency of gout attacks and tophus resolution did not differ significantly from those of probenecid, (although only a small number of patients presented with tophi): Both groups improved on these measures from baseline. The allopurinol group experienced a mean reduction in serum urate from 9.3mg/dl to 4.7mg/dl by the last measurement, whereas serum urate in the probenecid group was reduced from 8.5mg/dl to 5.2mg/dl at the final measurement; the statistical significance of this difference was not stated. The groups did not appear to differ significantly in terms of adverse event frequency, but the nature of these events differed between the groups. All adverse events were deemed to be minor. The investigators did not stratify any of the data by subgroups (see Tables18 and 19).

Table 18. Systematic reviews of allopurinol versus probenecid for the management of chronic gout

Author/Year Funding	End Date of Search	# of Included Studies	# of Included Patients/ Participant Characteristics	Setting	Doses	Outcomes	Results	AMSTAR
Kydd, 2014[144]	May 2013	1 study compared probenecid with allopurinol	37 patients with chronic gout	"clinic"	Allopurinol 300mg daily, raised to 400mg or 600mg where necessary Probenecid 1 g daily, increased to 2 g after 2 weeks	Frequency of acute gout Tophi Serum urate Adverse events	Groups did not differ with respect to reductions in gout attacks, although both groups experienced a reduction. The few patients in the study that had tophi both experienced resolution. Decreases in serum urate were observed in both groups, but the decreases were greater for the patients taking allopurinol. Adverse events occurred in both groups.	9/9

Table 19. Randomized controlled trials of pharmacologic therapies for chronic gout not included in existing systematic reviews

Author/Year	Population, Sample Size	Intervention	Outcomes	Timing	Results	Cochrane ROB
Scott, 1966[145]	37 patients with chronic gout referred to "clinic"	Allopurinol 300mg daily, raised to 400mg or 600mg where necessary Probenecid 1 g daily, increased to 2 g after 2 weeks	Frequency of acute gout Tophi Serum urate Adverse events	2 weeks, 1 month, 2 months, 3 months, and 3 month intervals up to 24 months	Groups did not differ with respect to reductions in gout attacks, although both groups experienced a reduction. The few patients in the study that had tophi both experienced resolution. Decreased in serum urate were observed in both groups, but the decreases were greater for the patients taking allopurinol. Adverse events occurred in both groups.	1. Sequence: Low 2. Allocation concealment: High 3a. Blinding participants: High 3b. Blinding care providers: High 3c. Blinding outcome assessors: High 4a. Follow-up less than 20%: Low 4b. Loss to follow-up missing data explained: Low 4c. Only those who completed the treatment program 5. Outcome reporting: Low 6. Findings reported as % who responded: High

Prophylaxis Against Acute Gout Attacks (Flares) When Starting Urate Lowering Therapy

For nearly 50 years, it has been known that the initiation of urate lowering therapy is associated with an increase in the frequency of acute gout attacks (flares).[159] More than 30 years ago, investigators performed trials using colchicine as prophylaxis against acute attacks when starting uricosuric therapy.[74, 160] However, it was not until 2004 that the first randomized, placebo controlled trial of colchicine prophylaxis when initiating allopurinol therapy was published.[63] In this study, investigators randomized 51 patients to colchicine, 0.6mg twice daily, or placebo when starting allopurinol at 100mg once a day and titrating upwards with a target serum urate of 6.5mg/dl. Eight patients dropped out before they received any study drug. Seven patients withdrew during treatment: three in the colchicine group and four in the placebo group (two in the latter group due to a high frequency of attacks or flares). The 43 patients who completed the trial averaged approximately 63 years of age, mostly male, mostly (70 percent) white, more than 60 percent had tophi, and about 10 percent had chronic renal insufficiency. Patients were followed for 6 months. The occurrence of gout flares was recorded by patient recall at 3-month and 6-month visits. The difference in the reduction in flares between treatment groups was dramatic: Flares occurred in 77 percent of placebo-treated patients and 33 percent of colchicine-treated patients (p=0.008). During the first 3 months of treatment, placebo-treated patients averaged about 2 attacks (flares) and colchicine-treated patients averaged about 0.5 flares. From months 3 to 6, this advantage diminished somewhat, with about 1 flare per patient in the placebo group and almost no flares in the colchicine group. Diarrhea was much more common in colchicine-treated patients than in placebo-treated patients (43 percent vs. approximately 4 percent).

Since that study was conducted, and even pre-dating publication of this trial, the use of prophylactic therapy concomitant with the initiation of ULT has been the standard of care according to both EULAR and ACR guidelines.[31, 32, 161] All three of the recent large ULT trials—FACT, APEX, and CONFIRMS—used prophylaxis with colchicine or NSAIDs,[118-120] in spite of the fact that no randomized trials have assessed NSAIDs as a prophylactic therapy in this situation. In the FACT and APEX trials, where prophylaxis was given for 8 weeks, both trials showed spikes in the number of acute attacks (flares) concomitant with the discontinuation of prophylaxis (an approximate doubling of the proportion of patients reporting a flare, from 20 percent to 40 percent). CONFIRMS continued prophylaxis for the entire 6 months of the trial, and no spike in attacks (flares) occurred. Wortmann and colleagues collected the adverse event data from all three trials and pooled data for FACT and APEX.[148] It is important to note that in all three trials, patients were not randomized to different prophylaxis regimens; rather assignment was at the discretion of the treating physician. Hence, selection bias is potentially present. Overall adverse events were higher with colchicine prophylaxis than with naproxen prophylaxis (55 percent vs. 44 percent). Diarrhea was about three times more common with colchicine than with naproxen prophylaxis (8.4 percent vs. 2.7 percent). In CONFIRMS, no statistically significant difference was seen in overall AEs reported (about 55 percent in both colchicine and naproxen-treated patients), but gastrointestinal and abdominal pains were about three times more frequent in naproxen-treated patients (3.2 percent vs. 1.2 percent). Headache was more commonly reported in colchicine-treated patients. In all three studies, upper respiratory infection was the most frequently reported AE (8 percent-9 percent in each group, no statistically significant difference). In a 2014 SR that included the one RCT mentioned above,[63] plus four others that employed prophylaxis when initiating therapies not included in the scope of this review (rilonacept and canakinumab),

Latourte and colleagues concluded that low-dose colchicine and low dose NSAIDs are the two first-line options for prophylaxis, and that the choice depends on comorbidities and tolerance and potential interaction with other prescribed medications (AMSTAR of 3/9).[146] In another 2014 SR, on preventing acute gout attacks when initiating ULT, which was conducted as part of the 3e Initiative on the Diagnosis and Management of Gout, Seth and colleagues identified four placebo-controlled RCTs: the one study described above,[63] one described below,[55] one study included in a SR that we included,[74] and one study that used concomitant canakinumab, a drug not included in our scope. This review (AMSTAR of 7/9) concluded, like the other review and our assessment of the original trials, that colchicine prophylaxis for at least six months, when starting ULT, reduces the risk of acute attacks.[147]

The optimal duration of prophylaxis is unknown. Discontinuation of prophylaxis at 8 weeks is associated with a spike in attacks (flares) that does not occur when prophylaxis is continued for 6 months, but the report of the CONFIRMS trial did not describe whether flares spiked when prophylaxis was discontinued at 6 months.

We identified one RCT that compared different durations of colchicine prophylaxis when initiating allopurinol therapy in patients with gout.[55] In this study, 229 patients with gout who were beginning allopurinol therapy were randomized to receive colchicine therapy (1mg/day) for either 3-6 months, 7-9 months, or 9-12 months duration. The only clinical data presented about the patients is that they averaged 47 years of age, were overwhelmingly male, and had a mean pre-treatment serum urate level of 8.5 and an on-treatment serum urate level of 6.1mg/dl. The outcome measure was "any evidence of recurrence of gouty arthritis," but the criteria for this clinical event were not specified. Of the enrolled patients, 190 (82 percent) contributed data to the outcome. Loss to followup by group was not specified, but almost equal numbers of patients were included in each group at followup, so loss to followup was probably similar in each group. At both 6 months and 1 year, the proportion of patients who experienced recurrence was much higher in those randomized to 3-6 months of therapy than in those randomized to longer durations of therapy (at 6 months, 46 percent vs. 11 percent vs. 6 percent; at 1 year 54 percent vs. 27.5 percent vs. 23 percent, respectively). We judged this study as being at high risk of bias; therefore we could draw no conclusions from it.

Effect of Dietary Modification in Addition to Pharmacologic Therapy

The only randomized trial of dietary modification in addition to pharmacologic therapy tested specific dietary advice compared with general dietary advice.[106] No difference was seen in serum urate between groups. The trial is discussed in more detail in KQ 2.

Strength of Evidence

Urate Lowering Therapy and Short Term Changes in Acute Gout Attacks

We judged the strength of evidence as high that urate lowering therapy does not reduce the risk of acute gout attacks, up to about six months, based on two placebo-controlled trials that each reported no difference in that outcome between groups.

Urate Lowering Therapy and Longer Term Changes in Acute Gout Attacks

No placebo controlled RCTs examined acute gout outcomes longer than six months from initiation of therapy. Nevertheless, we judged the strength of evidence as moderate that urate lowering therapy reduces the risk of acute gout attacks, based on the RCT evidence that urate lowering therapy reduces serum urate, the primary role of elevated serum urate as a risk factor for acute gout attacks, and the results of open-label extensions of the urate lowering therapy trials that show a steadily decreasing risk for acute gout attacks and a sustained decrease in this risk after about 1 year of therapy (< 5 percent/year).

Prophylactic Therapy

Although only one placebo-controlled trial tested the efficacy of prophylactic therapy when starting urate lowering therapy, we judged the strength of evidence as high that such therapy reduces the risk of acute gout attacks. We base this assessment on the large size of the effect in this trial (of colchicine), and the evidence from three large RCTs of urate lowering therapy.

In two of these trials, prophylaxis was given for eight weeks, and discontinuation of prophylaxis was accompanied by a sudden two-fold increase in the risk of acute gout attacks. In the third trial, prophylaxis was continuous throughout the six-month trial, and no "spike" of flares occurred.

Duration of Prophylaxis

We judge the strength of evidence as moderate that a course of prophylaxis longer than eight weeks is more effective than one of eight weeks duration based primarily on a comparison of acute gout attacks in the three ULT trials described above. This assessment is also supported by one RCT with high risk of bias.

Addition of Dietary Advice

We judged the strength of evidence as insufficient that the addition of gout-specific dietary advice adds to the effectiveness of urate lowering therapy, based on the existence of only one small RCT at high risk of bias.

Key Question 4: Treatment Monitoring of Patients with Gout

a. In adults with gout, does monitoring serum urate levels with pharmacologic treatment and/or dietary and/or lifestyle change measures (e.g., compliance) improve treatment outcomes?

b. Is achieving lower subsequent serum urate levels (less than 5 vs. 5–7mg/dL) associated with decreased risk for recurrent acute gout attack, progression to chronic arthritis or disability, resolution of tophi, or other clinical outcomes (including risk for comorbidities or progression of comorbidities) or patient-reported outcomes?

Key Points

- Evidence is insufficient to support or refute that monitoring serum urate improves outcomes.

- Low-strength evidence supports the finding that treating to a specific target serum urate level reduces the risk of gout attacks. However, the only way to know if urate lowering therapy affects serum urate is by monitoring serum urate levels. Therefore, this logic supports some monitoring, although how often and to what target have not been experimentally tested.

Description of Included Studies

For KQ4a, we include one SR[162] from which 16 original studies were reference mined.[163-178] For KQ4b, we identified one SR[179] and eight studies that addressed the question.[11, 180-186]

Detailed Synthesis

a. In adults with gout, does monitoring serum urate levels with pharmacologic treatment and/or dietary and/or lifestyle change measures (e.g., compliance) improve treatment outcomes?

Our literature search identified one SR of studies assessing factors associated with medication adherence in gout (AMSTAR rating of 5 out of 9).[162] This study searched multiple databases through July 2013 and supplemented this search with hand searches and Google scholar. Inclusion criteria were a patient population with gout, measurement and/or reporting of medication adherence, and publication in one of three languages. Data from RCTs were excluded as not being representative of real-world patient settings. From 1,398 titles, the authors identified 16 studies. We retrieved these studies and reviewed them to see if the investigators assessed the association between monitoring serum urate levels and compliance. Eleven studies did not test for the effect of serum urate on compliance.[165-167, 169, 171, 172, 174, 176-178, 187] Four studies did assess serum uric acid, but analyzed whether measures of compliance were associated with subsequent serum urate levels.[163, 168, 173, 188] One study tested the effect of serum "uric acid measurements" on compliance.[175] This analysis included 9,823 Medicare patients who had a pharmacy benefit via the Pennsylvania Pharmacy Assistance Contract for the Elderly. The measure of compliance was the Percentage of Days Covered, which the authors claimed is nearly identical to the more commonly used Medication Possession Ratio. A value of 80 percent was used as the threshold between compliance and non-compliance. A number of factors were considered as possible predictors of noncompliance, including socio-demographic variables and "gout specific factors." The latter included uric acid measurements. This factor was not a statistically significant predictor of compliance, an observation confirmed by contacting the first author of the paper, who said, "We found no evidence that performing tests was associated with adherence" (DH Solomon, personal communication, Jan 30th, 2015).

We performed an update search, using the authors' search strategy, from May 2013 to January 2015, and identified an additional 115 titles. Applying the same inclusion/exclusion criteria yielded no new studies assessing the effect of serum urate measurement on compliance or outcomes.

We identified no studies that assessed whether monitoring serum urate levels for gout patients influences treatment outcomes.

Summary

We found no evidence to support or refute the hypothesis that monitoring gout patients on treatment with serum urate measurements leads to improved compliance or improved outcomes. However, the only way to know if ULT is having an effect on serum urate is by monitoring serum urate levels, and this logic supports some monitoring, although how is unknown.

b. Is achieving lower subsequent serum urate levels (less than 5 vs. 5-7mg/dl) associated with decreased risk for recurrent gout attack, progression to chronic arthritis or disability, resolution of tophi, or other clinical outcomes (including risk for comorbidities or progression of comorbidities) or patient reported outcomes?

A large body of evidence supports the hypothesis that lower serum urate levels are causally associated with a lower rate of acute gout attacks (flares). Underlying this hypothesis is the basic chemistry of uric acid, namely that it is soluble up to a concentration of about 6.8mg/dl, above which it may start to precipitate. However, patients with serum urate levels above this threshold may still be asymptomatic whereas gout patients with serum urate levels below this threshold still may have acute attacks (flares).

The best data on the relationship between serum urate levels and risk of acute attack may come from analyses of the large trials of ULT, FACT and APEX. In a post-hoc analysis that combined data from both of these trials, and that included more than 1800 subjects with gout and a baseline serum urate level of 8.0mg/dl or greater, the achieved serum urate level was one of three variables (along with the baseline presence of tophi and the percent change in serum urate level from baseline) that, in multivariate logistic regression, was associated with acute gout attacks (flares) requiring treatment (adjusted odd ratio of 1.42 [95% CI 1.16, 1.73] and adjusted odds ratio of 2.70 [95% CI 1.72, 4.22], at either 6 months or 12 months after initiation of therapy, respectively).[182] When the serum urate level achieved was dichotomized at 6.0mg/dl, at the end of one year, those patients, that had achieved a value below 6.0mg/dl, regardless of treatment group, had acute gout attacks (flares) at a rate of approximately 5 percent, whereas this rate was between 10 percent and 15 percent for patients with serum urate levels at or above 6.0mg/dl (p value reported as less than 0.05).

Supporting the results of this trial are the findings many retrospective cohort studies. Although not all of these studies restricted the eligible patients to those with gout on ULT, we nevertheless deemed their results relevant for this study question. For example, among 2237 patients aged 65 and older in the Integrated Healthcare Information Services claims database between 1999 and 2005were 633 patients with gout and a serum urate level less than 6mg/dl, 1,173 persons with a serum urate level between 6.0 and 8.99mg/dl, and 431 patients with a serum urate level of 9.0mg/dl or greater. The proportions of patients among these three groups with at least one gout flare over a 12-month period, as defined by a visit for gout and receiving a prescription for typical acute gout pharmacologic therapy, were 27 percent, 43 percent, and 46 percent, respectively.[180]

In another study, patient-level data were collected from 125 rheumatologists and 124 primary care providers in the US. Data on 1,245 patients with gout were analyzed. Serum urate level was positively correlated with the occurrence of a gout flare over 12 months (r=0.29, p value reported as less than 0.01) [185]

In another study of similar design, patient-level data were collected from 50 U.S. practices on recent patients with gout seen from 2010 to 2011. Of 479 patients assessed, serum urate level was associated with a flare-related visit in bivariate analyses (p=0.004).[184]

Two other administrative claims analysis studies, one including 18,243 patients and the other including 5,942 patients, both of which used algorithms involving claims and pharmacologic prescriptions to identify gout patients, reported that patients with a serum urate level of greater than 6.0 had 1.3 times the odds of an acute gout flare[181] or a 1.59 relative risk.[183]

A SR (AMSTAR rating 7 of 9) identified 11 studies that assessed the association among allopurinol administration, serum urate levels, and subsequent outcomes; subsequent gout attacks were the outcomes in seven of the 11 studies. None of the included studies were experimental. Six were cohort studies, three were administrative database analyses, and two were case control studies. All of the studies were judged as being at high risk of bias, thus limiting any conclusions that could be drawn. Nevertheless the authors concluded that reductions in serum urate (SUA) "are significantly associated with the achievement of desirable gout outcomes." However, the authors caution that the "the level to which SUA must be reduced (cut off point) remains unclear."[179]

Few studies have related serum urate levels to comorbidities. One study of U.S. Veterans with gout used the VA data warehouse to follow 2116 patients for a mean followup of 6.5 years. Comparing patients with high versus low serum urate levels, the investigators reported about a two-fold difference in new diagnoses of kidney disease (4 percent vs. 2 percent at year 1, 9 percent vs. 5 percent at year 3, respectively).[11] However, this study had a high risk of bias.

Lastly, an abstract presented by investigators at the Mayo Clinic described a study that followed 158 patients with incident gout (mean serum urate level was 8.1mg/dl; 70 percent of cases presented as podagra) in Rochester MN for a mean of 13 years. . Higher serum urate levels predicted a subsequent acute gout flare (odds ratio 1.35, 95% CI 1.2, 1.5). However, only 70 percent of the patients had a flare during the extended followup, meaning that 30 percent of patients had only the single incident episode .[189]

Limiting the evidence base for using serum urate as a target value for treatment, (as blood pressure and hemoglobin A1c are used, for example, for the management of hypertension and diabetes), is the lack of any experimental study that has based treatment decisions on a target. Treating to a target necessarily means increasing doses of medication, which increases the risk of side effects, and therefore changes the benefit: risk assessment.

Strength of Evidence

Monitoring Serum Urate Levels

Evidence is insufficient for an effect of monitoring serum urate levels. An argument can be made that without monitoring, treatment cannot be adjusted.

Treating to Target

The strength of evidence is low that treating to a specific serum urate level reduces the risk of acute gout attacks. While elevated serum urate is the primary risk factor for acute gout attacks, and lowering serum urate levels can be expected to reduce the risk of acute gout attacks, the concept of a specific target value, such as 6.0mg/dl, has not been tested. Different targets have been proposed (e.g., 7.0mg/dl, 6.0mg/dl, 5.0mg/dl) and trying to lower serum urate levels to a target in patients who may be asymptomatic (in that they have not had a recent acute gout attack) at higher-than-target levels will necessitate increasing use of medication. The value of that strategy has yet to be

proven, and examples exist from other asymptomatic conditions, in which treating to target resulted in more side effects than benefit. Thus, despite the strong biologic appeal of such a strategy, we judged the strength of evidence as low.

Key Question 5: Discontinuation of Pharmaceutical Management for Patients on Acute or Chronic Gout Medications

In adults with gout, are there criteria that can identify patients who are good candidates for discontinuing

a. urate lowering therapy?

b. anti-inflammatory prophylaxis against acute gout attack for patients on urate lowering therapy after an acute gout attack?

Key Points

- The evidence is insufficient that discontinuing urate lowering therapy results in no increase in risk of acute gout attacks in gout patients who have completed 5 years of urate lowering therapy that kept serum urate levels < 7mg/dl, and in whom subsequent annual serum urate levels (off of urate lowering therapy) stayed < 7mg/dl.
- Moderate-strength evidence supports the finding that prophylaxis for acute gout with low dose colchicine or NSAIDs when initiating urate lowering therapy results in fewer gout attacks when treatment is given for longer than 8 weeks.

Description of Included Studies

We identified three observational (prospective cohorts) studies that assessed two clinical cohorts of patients in whom urate lowering therapy was discontinued.[190-192]

The data about duration of anti-inflammatory prophylaxis when initiating urate lowering therapy comes from the results of the FACT, APEX, and CONFIRMS trials, previously discussed in detail in response to KQ4.

Detailed Synthesis

Discontinuation of Urate Lowering Therapy

We identified three prospective observational cohort studies of patients in whom ULT was discontinued and patients were followed for an extended period of time.[190-192]

More than 30 years ago, Loebl and Scott followed 33 patients with gout on allopurinol. All but one patient was male, their mean age was 58, and none of the patients were overproducers of uric acid as assessed by 24-hour urinary uric acid analysis. The mean serum urate level before treatment was 8.4mg/dl, decreasing to 5.5mg/dl while on therapy. Patients were on therapy for a mean of 93 weeks before discontinuation. They were followed for a mean of 86 weeks off therapy. In all patients, serum urate levels rose quickly following discontinuation of therapy. However, only 12 patients (36 percent) experienced a recurrence; the other 21 patients remained asymptomatic during the period of observation. Twenty of these patients continued off allopurinol at a mean of 107 weeks. The main difference between symptomatic and asymptomatic patients

was their serum urate level on therapy: 6.2mg/dl in the symptomatic patients and 5.1mg/dl in those who were asymptomatic (statistical testing was not performed).[191]

In the second study, Perez-Ruiz and colleagues[190] assembled a cohort of 211 patients with gout who met the following criteria:

- An average serum urate level of <7mg/dl for "the entire duration of " ULT
- Compliance with ULT for 5 years, or 5 years after resolution of any tophi. Compliance was defined as ≥ 80 percent of all serum urate levels <6mg/dl during therapy.

Patients were overwhelming male and averaged 65 years of age. About 25 percent had subcutaneous tophi at baseline. Mean pre-treatment serum urate levels were 8.0mg/dl, the mean duration of ULT was 66 months, the mean serum urate level on therapy was 4.9mg/dl, and the mean serum urate level following discontinuation of therapy was 8.5mg/dl. The mean followup time was 33 months. Among the 27 patients who maintained a serum urate level less than 7mg/dl off therapy, none had a clinical recurrence. Of the remainder, clinical recurrences were highly correlated with off-treatment serum urate levels: 13 percent of 61 patients with a value of 7.0-8.2mg/dl, 51 percent of 61 patients with a value of 8.2-9.3mg/dl, and 61 percent of 62 patients with a serum urate level about 9.3mg/dl. These results confirmed the findings of an earlier report by the same author, of about 100 patients, some or all of whom probably contributed data to their cohort of 211. In the earlier paper the median "survival" off ULT to the first acute gout attack was 34 months for patients with higher SUA (≥ 8.75 mg/dl) and 49 months for patients with lower levels (≤ 5.05 mg/dl).[192] The authors speculate that a period of 5 years of "crystal depletion" with a target serum urate level "far below" 6mg/dl, could be followed by more relaxed, or even no therapy, designed to keep serum urate levels less than 7mg/dl.

Discontinuation of Prophylaxis

In FACT and APEX, anti-inflammatory prophylaxis was discontinued after 8 weeks and in both studies, acute gout flare spiked immediately thereafter (about double the rate). In CONFIRMS, anti-inflammatory prophylaxis was continued for 6 months, to the conclusion of the trial, and no spike occurred at 8 weeks.

One older 1989 trial of intermittent ULT concluded that intermittent therapy was less effective than continuous therapy. This study did not use true random assignment and therefore did not meet our eligibility criteria; however, we have included it, as it is the only trial of its type. This study assigned 50 patients by the even/odd hospital number to either continuous allopurinol (titrated to a dose of about 300mg/day) or 8 weeks cycles on and off allopurinol. In the first two years of therapy, the number of acute gout attacks did not differ statistically significantly between groups, but up to 4 years after therapy, attacks were more common in the intermittent treatment group (10 attacks) than in the continuous treatment group (0 attacks).[193]

Strength of Evidence

Discontinuation of ULT

We judged the strength of evidence as insufficient that patients who were asymptomatic for five years with a serum uric acid of <7mg/dl could have their ULT discontinued. Only one cohort study, which enrolled more than 200 patients with gout, found evidence supporting discontinuation of medication. This strategy will need to be tested in an RCT. Selection bias is always a concern in observational studies of treatment strategies.

Prophylactic Discontinuation

A moderate strength of evidence supports the finding that prophylaxis longer than eight weeks is associated with better outcomes than prophylaxis of eight weeks duration, based on the cross-study comparison of risk of acute gout in three urate lowering therapy trials.

Discussion

Key Findings and SoE

We found a large number of research studies about gout, yet only a relatively modest number of these studies provided evidence for some of our KQs, particularly for the treatment of acute gout: only a single placebo-controlled trial of NSAIDs for acute gout pain, two placebo controlled RCTs of colchicine, and none at all for corticosteroids or ACTH. Nevertheless, we were able to reach strong conclusions about the usefulness of these drugs because of some specific features of gout: Symptoms result from an inflammatory reaction to the deposition of urate crystals, which occurs when serum urate rises above its saturation point in the blood. Hence, in an era that predated the widespread practice of placebo-controlled trial testing of therapies, medications aimed at blocking the inflammatory response were tried as treatments. Steroids are one of the most powerful and effective anti-inflammatory medications available. Although no placebo-controlled RCTs have tested their use in acute gout, steroids have proven efficacy in other inflammatory conditions, which gives us confidence that they are effective in treating the inflammatory reaction in acute gout. At this point, a placebo-controlled trial of steroids in acute gout may well be unethical, as it would mean withholding therapies of known effectiveness (e.g., colchicine) from the placebo-treated group. Indeed, a recent, high profile study of the use of steroids in acute gout compared their use not to placebo, but to NSAIDs. Because NSAIDs also have no conclusive placebo-controlled trial evidence of their effectiveness in acute gout, could it be that this RCT, which found only minor differences in outcomes between the two treatments, actually was comparing two treatments that were equally ineffective? We think not. We believe that both drugs are effective in treating acute gout, and therefore judged the SoE as high that their use relieves symptoms by a clinically important amount—despite the lack of placebo-controlled RCT evidence.

With regard to chronic gout, we similarly used evidence from a number of sources to reach conclusions about the effectiveness of ULT at reducing the risk of acute gout attacks over time, despite the fact that this outcome has not been studied in any placebo-controlled trial of longer than a few months. We based our moderate SoE rating on the high strength evidence that ULT reduces serum urate, that serum urate level is a strong predictor of the risk of acute gout attacks, and that the open-label extension studies of randomized controlled trials of ULT have shown a graded relationship between the serum urate level achieved and the risk of acute gout attacks. We thus concluded that over time, possibly by 1 year from initiation of therapy, ULT reduces the risk of acute gout attacks. We also concluded, based on a comparison of the timing of the occurrence of acute gout attacks in the weeks following initiation of ULT, that longer courses of prophylactic treatment with colchicine or NSAIDs (greater than 8 weeks) are more effective than courses of treatment with durations of 8 weeks or less, since in the one RCT of urate lowering therapy where prophylactic colchicine or NSAIDs were continued for 6 months, no “spike” in acute gout attacks coincided temporally with the discontinuation of the prophylactic therapy, like that seen in other RCTs where prophylaxis was stopped at 8 weeks.

A third key finding of our review is that there is scant direct evidence about how much ULT to give (e.g. the concept of treating-to-a-target) and for how long to give it (are there any criteria about when ULT can be stopped, or if once started is treatment needed for life?).

The key findings and SoE are in Table 20.

Findings in Relationship to What is Already Known

In general, our findings support the results of existing SRs. We did find a number of RCTs not included in prior reviews. Some of these studies were "first-of-their-kind," such as those testing a specific dietary therapy and the duration of colchicine prophylaxis. However, most new studies either confirmed prior knowledge, or, in the case of studies of novel treatments, were not sufficiently high quality for us to draw conclusions.

Applicability

Of the 115 studies assessed in detail (not counting SRs), only 9 studies explicitly stated that patients came only from, or the study included patients from, primary care sites (including the ED and urgent care settings). Furthermore, it is likely that patients enrolled in clinical trials differ from those commonly seen in primary care settings. In the major trials of ULT, the proportion of patients with tophi is greater than 20 percent[118-121] whereas in a trial that explicitly enrolled patients from primary care, the proportion of patients with tophi was 10 percent. A population-based study of more than 50,000 gout patients in English primary care practices reported the proportion with tophi as 0.5 percent[194] Patients enrolled in clinical trials usually have fewer comorbidities than those seen in practice, because clinical trials have exclusion criteria. Thus, in most trials, enrolled patients probably had more advanced gout, but were better on average with respect to their other health conditions, than patients typically seen in primary care settings. We thus judged this evidence of moderate applicability to primary care.

Implications for Clinical and Policy Decisionmaking

The implications of this review for clinical decision-making follow from the identification of which interventions for gout management have evidence of an effect on clinical outcomes, either directly or through a strong indirect evidence chain. Thus, the results in Table B will be useful in policy decision-making and in the development of practice guidelines.

Limitations of the Comparative Effectiveness Review Process

For many of the KQs of interest, data were not reported on the subgroups or outcomes of interest as specified in the KQs and analytic frameworks, limiting the comparative effectiveness review. For the portion of the review on Traditional Chinese Medicine (TCM), the variability in tested interventions made comparisons across studies not justified.

Limitations of the Evidence Base

The lack of studies specifically stating that they enrolled patients in primary care settings is a limitation, as is the lack of randomized controlled studies assessing clinical outcomes for ULT (such as recurrent acute gout flare after 1 year) and intervention studies of dietary therapies for management of chronic gout. Longer term studies will be needed to assess the degree to which ULT reduces acute gout attacks relative to the adverse events of long term use of the available medications.

Research Gaps

The concept of "treat-to-target" (TTT) in gout, while supported by indirect evidence, has been untested. Guidelines and recommendations about TTT thresholds already vary, for example, <

6mg/dL for all gout patients versus < 5mg/dL for patients with significant gout morbidity. However, for many gout patients in primary care practice whose gout is well controlled on ULT, no data support such targets. In fact, the results of one cohort study suggest that once gout has been asymptomatic for 5 years, ULT might be discontinued for many years (as long as serum urate levels remain acceptable, e.g., < 7mg/dL).[190] Therefore, the most important research gap is a RCT comparing different TTT levels in patients with gout and elevated serum urate.

Treatment decisions are likely to be preference-sensitive, and studies are needed to assess patient preferences for different outcomes (for example, to what degree do patient preferences differ for outcomes such as a decrease in risk from 2 percent to 0.5 percent for an acute gout attack in the coming year versus a 5 percent chance of a skin rash and a less than 1 percent chance of a very serious skin rash).

Likewise, in spite of the many observational studies linking dietary factors with risk for gout, few studies have assessed the effect of specific dietary advice. Some dietary advice, such as generic advice to lose weight in overweight and obese patients, has evidence of benefit for other conditions and can be advocated in gout patients without additional data (e.g., it is always indicated to recommend dietary weight loss in patients who are obese). But primary care providers could more confidently recommend gout-specific dietary advice if compelling evidence supported an effect of such dietary changes on the risk for gout attacks or other gout-related outcomes. Therefore, another important research gap is evidence from RCTs for specific dietary changes (such as reducing or eliminating sugar-sweetened beverages or high-fructose foods, adequate hydration, restriction of alcohol, increase in low fat dairy consumption, and even restriction of high purine foods) compared with standard healthy diet advice and weight loss in reducing the risk of gout attacks.

A third research gap is the better characterization of adverse events from ULT and how they may be minimized. If the rare but serious adverse events from ULT could be further minimized, for example by HLA typing for predisposition, then the benefit/risk profile of ULT would further improve and make more patients eligible for treatment.

An additional research gap concerns prophylaxis when initiating ULT therapy. The optimal duration of such therapy has not been experimentally tested, and the comparative benefits/risks of all three agents used for acute attacks (colchicine, NSAIDs, oral steroids) have not been established.

Conclusions

Several drugs show moderate-to-high evidence of benefit in terms of reducing pain in patients with acute gout. It is clear that urate lowering therapy achieves its goal of lowering urate levels. Decreased serum urate should lead, over time, to a reduction in gout attacks, but the benefits and harms of long term urate lowering therapy have yet to be demonstrated directly. Patient preferences are likely to be important in decision-making (as specified above), and having better estimates of the size of the benefit of urate lowering therapy will make clinicians and patients more knowledgeable about the risk: benefit trade-off for the different decisions.

Table 20. Summary of prior knowledge, findings from the systematic review, and strength of evidence, by KQ

Key Question	Prior Knowledge Used in Determining Strength of Evidence	Sources of Evidence Included in This Systematic Review	Strength of Evidence
KQ1 Acute Gout Treatment			
Colchicine reduces pain	N/A	• 2 placebo-controlled RCTs (N=45 and N=184) both with low risk of bias	High
Low-dose colchicine is as effective as higher dose for reducing pain, with fewer side effects	N/A	• 1 head-to-head RCT with low risk of bias (N=184)	Moderate
NSAIDs reduce gout pain	• Biologic rationale (anti-inflammatory action) • Placebo-controlled RCT evidence that NSAIDs provide temporary pain relief for numerous conditions	• 1 placebo-controlled RCT with high risk of bias (N=30) • High strength observational data (NSAID use as prophylaxis against gout flare) (see below under KQ3)	High
No difference between NSAIDs in effectiveness	• Equivalence in effectiveness among NSAIDs in numerous other conditions	• 16 head-to-head RCTs	Moderate
Systemic corticosteroids reduce pain	• Biologic rationale (anti-inflammatory action)	• No placebo-controlled RCTs • Equivalence to NSAIDs in 4 RCTs (N=27, N=90, N=120, and N=60).Three of four RCTs had low risk of bias.	High
Animal-derived ACTH formulation reduces pain	• Biologic rationale (anti-inflammatory action)	• No placebo-controlled RCTs • Equivalence to NSAIDs and intramuscular steroids in RCTs (one RCT of each, N=76 and N=31 both at high risk of bias)	Moderate
Differences stratified by patient demographic, comorbid conditions, disease severity, clinical presentation, or laboratory values	N/A	None of the included RCTs presented data stratified by these variables.	Insufficient
KQ2 Diet and lifestyle management			
Specific dietary changes (including reducing intakes of dietary purines, protein, or alcohol; increasing intakes of cherries, modified milk products, or supplemental vitamin C; or achieving weight loss) in gout management may affect symptomatic outcomes	N/A	• 3 RCTs (two at high risk of bias) (N=67, N=120, N=40) • 3 observational studies (N=20, N=120, N=633)	Insufficient

Key Question	Prior Knowledge Used in Determining Strength of Evidence	Sources of Evidence Included in This Systematic Review	Strength of Evidence
Gout-specific dietary advice (counseling about reducing red meat; avoiding offal, shellfish, and yeast-rich foods and beverages or increasing low-fat dairy products, vegetables, and cherries) compared with nonspecific dietary advice (counseling about the importance of weight loss and reduced alcohol intake) for reducing serum urate levels in patients with gout	N/A	• 1 RCT with high risk of bias (N=30)	Insufficient
Effectiveness of Traditional Chinese Medicine (TCM) (acupuncture, herbal mixtures, moxibustion) on symptomatic outcomes	N/A	• 86 RCTs, all of idiosyncratic therapies, with conflicting results	Insufficient
KQ3 Management of hyperuricemia			
Urate lowering therapy does not reduce the risk of acute gout attacks within the first 6 months	N/A	• 2 placebo-controlled RCTs,with low risk of bias (N=1,072 and N=57)	High
Urate lowering therapy reduces the risk of acute gout attacks after 1- year	• Acute gout attacks are caused by elevated serum urate concentrations	• No placebo-controlled RCTs assess long-term risk of acute gout attacks • RCTs with low risk of bias show that ULT reduces serum uric acid • Open label extension study of ULT RCT shows reduced risk of acute gout attacks over time, plateauing at less than 5% at about 1 year	Moderate
Urate lowering therapy reduces serum urate	N/A	• 4 placebo-controlled RCTs all with low risk of bias (N=1,072, N=96, N=153, and N=57)	High
40 mg febuxostat and 300mg allopurinol show no differences in serum urate lowering	N/A	• 1 head-to-head RCT with low risk of bias (N=2,269)	High
Effectiveness and comparative effectiveness of allopurinol and febuxostat depending on the presence of tophi	N/A	• Subgroup analyses of included trials did not report consistent results when stratified on the presence of tophi.	Insufficient
Age and race (Caucasian vs. African-American) do not affect the efficacy of febuxostat or allopurinol.	N/A	• Subgroup analyses of 1 head-to-head RCT with low risk of bias (N=2,269)	Low
Prophylactic therapy with low-dose colchicine or low-dose NSAIDs when beginning urate lowering therapy reduces the risk of acute gout attacks	N/A	• 1 placebo-controlled RCT of colchicine with low risk of bias (N=43) • Strong observational evidence across 3 RCTs with low risk of bias that included different durations of prophylaxis (N=762, N=2,269, and N=1,072)	High

Key Question	Prior Knowledge Used in Determining Strength of Evidence	Sources of Evidence Included in This Systematic Review	Strength of Evidence
Longer durations of prophylaxis with colchicine or NSAIDs (> 8 weeks) are more effective than shorter duration when initiating urate lowering therapy	N/A	• Indirect evidence from comparisons across 3 RCTs of differing durations of prophylaxis • 1 RCT with high risk of bias (N=190)	Moderate
Specific gout-dietary advice to reduce red meat, shellfish, etc. while increasing low-fat dairy products, vegetables, and cherries does not add to the effectiveness of urate lowering therapy for reducing serum urate	N/A	• 1 RCT with high risk of bias (N=30)	Insufficient
KQ4 Treatment Monitoring			
Serum urate monitoring improves outcomes	N/A	• No direct evidence • An argument can be made indirectly, based on the evidence that elevated serum urate levels cause gout	Insufficient
Treating to a specific target serum urate level reduces the risk of gout attacks	Lower serum urate levels are associated with reduced risk of gout attacks	• No RCT evidence • Variable targets proposed or assessed in the literature	Low
KQ5 Criteria for discontinuation of pharmaceutical management			
Hyperuricemia Urate lowering therapy may be discontinued in gout patients with 5 years of urate lowering therapy keeping serum urate levels <7mg/dl, with subsequent annual off-urate lowering therapy-serum urate levels <7mg/dl	N/A	• 3 prospective cohort studies (N=211, N=33, N=100)	Insufficient
Prophylaxis Prophylaxis for acute gout when initiating urate lowering therapy with low-dose colchicine or NSAIDs should be longer than 8 weeks	N/A	• Indirect evidence from comparisons across 3 RCTs with low risk of bias of differing durations of prophylaxis (N=762, N=2,269, and N=1,072)	Moderate

FDA = Food and Drug Administration; N/A = not applicable; NSAID = nonsteroidal anti-inflammatory drug; RCT = randomized controlled trial; ULT = urate lowering therapy

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Abbreviations/Acronyms

3e	Evidence, Expertise, Exchange
ACR	American College of Rheumatology
ACP	American College of Physicians
ACTH	Adrenocorticotropic Hormone
AE(s)	Adverse event(s)
AHRQ	Agency for Healthcare Research and Quality
ALL	Allopurinol
BMI	Body Mass Index
CI	Confidence interval
CT (Scan)	Computerized tomography
CVD	Cardiovascular disease
DASH	Dietary Approaches to Stop Hypertension
DNTT	Danggui-Nian-Tong Tang
eGFR	Estimated glomerular filtration rate
EPC	Evidence-based Practice Center
FEB	Febuxostat
GC	Glucocorticoid
GI	Gastrointestinal
GMP	glycomacropeptide
HRQoL	Health Related Quality of Life
KQ	Key Question
MD	Mean difference
MSU	Monosodium urate
NHANES	National Health and Nutrition Examination Survey
Non-GI	Non-gastrointestinal
NSAIDS	Nonsteroidal anti-inflammatory drugs
OR	Odds Ratio
PCPs	Primary care physicians
PICOTS	Populations, Interventions, Comparators, Outcomes, and Timing
PLB	Placebo
RR	Relative risk
SCEPC	Southern California Evidence-based Practice Center
SMD	Standardized mean difference
SMP	Skim milk powder
SRs	Systematic Reviews
sUA	Serum urate
TCM	Traditional Chinese Medicine

TEP	Technical Expert Panel
UA	Uric acid
ULT	Urate Lowering Therapy
US	United States
VA	Veterans Administration
XOI	Xanthine oxidase inhibitor

Appendix A. Search Strategy

DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 1/1/2010-4/23/2015

SEARCH STRATEGY:
"Gout"[Mesh] OR gout[tiab] OR gouty[tiab] OR toph*

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DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 1/1/2010-4/23/2015

SEARCH STRATEGY:
Gout suppressants[mh]
NOT
"Gout"[Mesh] OR gout[tiab] OR gouty[tiab] OR toph*

==========

DATABASE SEARCHED & TIME PERIOD COVERED:
Embase – 1/1/2010-4/23/2015

SEARCH STRATEGY:
gout:de,ab,ti OR gouty:de,ab,ti OR toph*:de,ab,ti
AND
[humans]/lim
AND
[embase]/lim
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DATABASE SEARCHED & TIME PERIOD COVERED:
Web of Science Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH – 1/1/2010-4/23/2015

SEARCH STRATEGY:
TS=(gout OR gouty OR toph*)
NOT
ts=(Aicardi-Goutieres)

==========

DATABASE SEARCHED & TIME PERIOD COVERED:
Cochrane Databases – 1/1/2010-4/23/2015

SEARCH STRATEGY:
'gout OR gouty OR toph* in Title, Abstract, Keywords

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FORWARD SEARCHES ON THE FOLLOWING ARTICLE:
EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR standing committee for international clinical studies including therapeutics (ESCISIT)
By:Zhang, W; Doherty, M; Bardin, T;Pascual, E; Barskova, V; Conaghan, P; Gerster, J; Jacobs, J; Leeb, B; Liote, F
Annals Of The Rheumatic Diseases, Volume: 65, Issue: 10, Pages: 1312-1324
Published: OCT 2006

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DATABASE SEARCHED & TIME PERIOD COVERED:
Web of Science – 1/1/2010-4/23/2015

SEARCH STRATEGY:
CITED AUTHOR: (zhang w*) AND CITED WORK: (ann rheum dis) AND CITED YEAR: (2006)

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DATABASE SEARCHED & TIME PERIOD COVERED:
SCOPUS – 1/1/2010-4/23/2015

SEARCH STRATEGY:
AUTHOR-NAME(zhang w*) AND TITLE-ABS-KEY(gout) AND PUBYEAR > 2005
Select citations to this article

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DATABASE SEARCHED & TIME PERIOD COVERED:
CLINICALTRIALS.GOV - Earliest-4/23/2015

SEARCH STRATEGY:
CONDITION = "Gout"

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MANUAL FILTERING IN ENDNOTE TO REMOVE DUPLICATES, ANIMAL-ONLY STUDIES, "GOUT" AS FRENCH FOR "TASTE," "TOPHAT" (Re: GENETICS), HISTORICAL ACCOUNTS, AUTHORS NAMED "GOUT" OR "TOPH*

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CLINICALTRIALS.GOV

CONDITION = "Gout"
RECEIVED FROM: Earliest in database to 4/23/2015

Appendix B. List of Excluded Studies

Not Human (N=2)

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Study of risk factor(s) for gout that doesn't test possible treatment (N=18)

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